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# *Effect of Curcumin on Lipid Profile, Oxidative Stress and Blood Glucose in Experimental Dexamethasone-Induced Diabetes in Rats*

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***ABSTRACT***

**Background:** The present study was conducted to evaluate the effect of curcumin as a flavonoid antioxidant on serum lipid profile, oxidative stress, and blood glucose in experimental models of type 2 diabetes (DM2). **Methods:** Subcutaneous daily injection of dexamethasone (5 mg/kg/day) for a month was performed to induce DM2. For this purpose, 28 adult male Wistar rats were divided into four groups: healthy control group received dexamethasone carrier containing normal saline + ethanol 4% , diabetic control group took 5 mg/kg/day dexamethasone, diabetic group 1 underwent the treatment with 50 mg/kg/day curcumin, and diabetic group 2 underwent treatment with 100 mg/kg/day curcumin. Seven days after dexamethasone injection, curcumin (50 and 100 mg/kg/day) was administrated intraperitoneally for 23 days. At the end of one month, the fasting blood sugar (FBS) level was measured and recorded by glucometer. Later, after a 30-day period, the animals were anesthetized with ether and their blood samples were collected from the heart puncture to measure their serum triglyceride (TG), high density lipoprotein cholrsterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and malondialdehyde (MDA). **Results:** The findings showed that curcumin could decrease FBS ($P < 0.05$), LDL-C ($P < 0.01$), TG ($P < 0.001$), and MDA ($P < 0.001$) and increase HDL-C ($P < 0.001$) at the end of 30 days. **Conclusion:** These effects of curcumin can be mediated by increasing either the pancreatic secretion of insulin or releasing from insulin bonds as well as enhancing insulin receptor sensitivity. Moreover, it may prevent the glucose absorption, reduce the activity of 3-hydroxy- 3-methyl glutaryl- CoA reductase (HMG-CoA), or improve the function of liver and pancreas through potent antioxidant properties.

**Keywords:** *Curcumin; Diabetes; Dexamethasone; Rat*

## Introduction

In recent decades, the incidence of diabetes mellitus, especially type 2 diabetes (DM2) has been increasing throughout the world and it is believed that the growing prevalence of this disease

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will be accelerated over the next 15 years. Based on the national diabetes statistics report-2020, 10.5% of the US population have diabetes (Atlanta, 2020). In a study conducted by Mirzaei et al., the prevalence of diabetes was 14.1% in Yazd province, center of Iran (Mirzaei *et al.*, 2020).

Diabetes is a disease of the endocrine system, which exists in two different types. DM2, also called non-insulin dependent diabetes, is commonly found in over 40 years old and obese people. The most important feature of the pathogenesis of DM2 is insulin dysfunction associated with insulin resistance.

Diabetic complications can be divided into the microvascular and macrovascular categories (Kirpichnikov and Sowers, 2001). This increased incidence of such diseases is considered as the leading cause of mortality among diabetic patients (Avogaro *et al.*, 2004). Diabetic nephropathy is also one of the major causes of death due to diabetes (Longo *et al.*, 2012).

DM2 is associated with the occurrence of a phenomenon called insulin resistance, which in fact occurs following a period of long-term insulin resistance, during which glucose level remains within the normal range at the cost of increased insulin (Goldstein, 2002).

Synthetic drugs, apart from its beneficial effects, have no maximum efficiency, but have many side effects. In this respect, medicinal plants have shown fewer complications and can be added to different diets (Sumbul *et al.*, 2011).

Due to the growing prevalence of diabetes throughout the world and despite the efforts of medical science in the management of diabetic complications, medicinal plants and traditional medicine were employed extensively in recent years to control diabetes in different populations (Liu *et al.*, 2007). Since the late nineteenth century, extensive studies were conducted on the treatment of diabetes and respective complications using medicinal plants; for example, Ginger and Aloe vera (Ajabnoor, 1990). Among various plants of interest, turmeric (*Curcuma longa*) is a plant with useful properties .

Given the important role of oxidative stress in the development of these side effects, much research has been conducted on strengthening the antioxidant system and their effectiveness in preventing diabetic complications in humans and experimental models. As a result, many positive results were reported. Accordingly, the present study examined the effects of curcumin, as the main substance found in turmeric root. Several studies demonstrated anti-diabetic effects of curcumin (Chuengsamarn *et al.*, 2012a).

Curcumin is a yellow pigment derived from turmeric. Over the past few years, numerous studies demonstrated that curcumin exerts several anticancer effects in various types of cancers by suppressing cell proliferation and metastasis inducing cell death. Curcumin has a broad range of activities including antioxidant, anticarciogenic, anti-inflammatory, hypocholesterolemic, wound healing, antispasmodic, anticoagulant, antitumor, and hepatoprotective activities. Curcumin also exhibits protective effects against cancer formation. The antiproliferative effect of curcumin can be attributed to its ability to regulate protein kinases, cell cycle, and transcription factors including NF-kB. In a melanoma cell line, curcumin exhibited a potent antiproliferation effect by inhibiting the binding activity of NF-KB.

In these studies, the findings showed that curcumin prevented the death of beta cells, improving the function of beta cells (Chuengsamarn *et al.*, 2012b). One of the mechanisms for anti-diabetic effects of curcumin is the stimulation of PPAR gamma receptors, such as anti-diabetic drug of thiazolidinediones (Kuroda *et al.*, 2005). In animal models of type I diabetes (DM1), curcumin was able to lower complications of diabetes, such as cataracts (Suryanarayana *et al.*, 2005), glucose, and lipid (Sidhu *et al.*, 1999) as well as to accelerate diabetic wound healing (Majithiya and Balaraman, 2005).

Since curcumin has strong antioxidant properties, reactive oxygen species (ROS) such as superoxide radicals, hydroxyl radicals, and hydrogen peroxide play a pivotal role in the pathogenesis of diabetes. Therefore, we hypothesised that curcumin might have a protective role against this condition (Anwar and Meki, 2003, Bonnefont-Rousselot *et al.*, 2000). Consequently, the aim of this study was to

investigate the anti-diabetic effect of injectable curcumin at the doses of 50 and 100 mg/kg in the model of dexamethasone-induced diabetes in rats. To the best of our knowledge, no study has ever been carried out in this regard.

## Materials and Methods

The dried rhizomes of C. amada were obtained from Green Pharmacy, Yasuj, Iran. Rhizomes of C. amada were grounded to a powder using a pulverizer and screened for 20 min for getting different particle sizes. The different particle sizes of C. amada powder used for the experimentation were within the range of 0.05 to 0.5 mm. Standard curcumin was prepared from Merck Co. Germany. Ultrasonic horn (tip diameter of 20 mm) with 250 W rated output power and 22 kHz frequency obtained from Bandlin Co (Germany) were used for the extraction based on the Ultrasound-Assisted Extraction (UAE) approach. Water bath was placed around the extraction flask to ensure that the solvent reservoir temperature did not increase drastically. Ultrasonic horn was operated in pulse mode (5 s on followed by 5 s off) and hence the solvent was not heated much. During the extraction, 6 g of C. amada powder was mixed with 150 ml of solvent to keep the ratio of solute to solvent similar to the conventional extraction operation. The mixture was irradiated for 1h and samples were withdrawn at regular intervals for the analysis.

In the present research, the effects of curcumin were tested on 28 adult male Wistar rats, which were divided into four groups of seven as follows:

1. Healthy control group, receiving dexamethasone carrier containing normal saline + ethanol 4%
2. DM2 control group taking 5 mg/kg/day dexamethasone
3- DM2 group 1 under treatment with 50 mg/kg/day curcumin by subcutaneous injection for 23 days, which dexamethasone was injected after the seventh day
4- DM2 group 2 under treatment with 100 mg/kg/day curcumin by subcutaneous injection for 23 days, which dexamethasone was injected after the seventh day.

The study duration was 30 days. DM2 was developed using daily subcutaneous injection of 5 mg/kg/day dexamethasone for 30 days (Ogawa *et al.*, 1992).

The rats were weighed again after 30 days. At the end of this period, the animals were anesthetized with ether. The animal was fixed on autopsy tray and 5 ml syringe was inserted into the rat heart to take blood samples. The needle was removed and blood sample was emptied into the sterile and labeled blood collection tubes by inserting the syringe tip on the inner edge of the tubes. The tubes containing blood samples were centrifuged at 3000 rpm for 15 minutes to separate the serums that were then stored at -20 °C until testing the study factors, including serum triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), malondialdehyde (MDA), and blood glucose.

*Instrumentation*s: Spectroscopic analysis was carried out using Doublebeam Shimadzu recording UV-Visible Spectrophotometer (Kyoto, Japan) model 1601 with 10 mm path length matched quartz cells used for analytical purpose. Stock solutions of curcumin containing 100 mg/ml were prepared in methanol and its aliquots were transferred in a series of 10 ml volumetric flasks in varying fractions and their volumes were made with methanol to prepare different standard dilutions varying from 0.01 to 10 mg/ml. Curcumin 5 µg/ml solution was scanned using a UV spectrophotometer within the range of 200-800 nm. Methanol was used as blank. Wavelength corresponding to maximum absorbance of curcumin in methanol was observed at 421 nm.

*Preparation of blood samples:* Centrifugation at 3000 rpm for 15 minutes was used to separate the serums, which were stored at -20 °C for subsequent measurements.

*Measurement of biochemical parameters:* The samples for measurement of TG, HDL-C, and LDL-C were transferred to the laboratory of

Yasuj Shahid Beheshti Hospital, Iran using BT3000 auto analyzer device.

*Measurement of oxidative stress markers:* The basic principle of measuring MDA is the reaction between the product of lipid peroxidation, i.e., MDA and thiobarbituric acid (TBA). Absorption of pink complex resulting from this reaction at high temperature was read by spectrophotometer at a wavelength of 532 nm and the concentration was determined using the standard curve. The MDA concentration was calculated for MDA-TBA complex. The amount of plasma MDA was reported as μM/l.

*Data analysis:* The obtained data were analyzed in SPSS software through one-way ANOVA and Tukey's test. The differences were considered significant at P-value ≤ 0.05.

## Results

According to the results obtained from the current study, no significant difference was found between the groups in biochemical parameters at the study baseline. Comparison of the mean weight between the pre- and post- test groups showed no significant differences between different groups. However, the mean weight in diabetic control group was decreased by 10% at the end of the period compared to the baseline, but this weight loss was not statistically significant. In the healthy control and group treated with curcumin, the weight gain was 6.2% and 3.4%, respectively, but the differnce was not statistically significant. The mean serum glucose levels of diabetic control group revealed significant difference compared with other groups (**Figures 2A&B**). No significant difference was observed in the mean glucose level in the groups treated with curcumin at the doses of 50 and 100 mg/kg/day compared to the healthy controls. Evaluation of the mean LDL-C in the studied groups showed that the highest level of LDL-C was related to the diabetic control group. A significant difference was seen between the diabetic control group and other groups; this difference indicates the effect of curcumin on reducing LDL-C in diabetic animals (**Figure 2C**).

The highest mean level of serum TG was related to the diabetic control group and the least amount was observed in the healthy control group. In other words, dexamethasone-induced diabetes increased the serum TG levels (96.2 ± 6.7 mg/dl). In addition, the mean serum TG levels in the groups 1 and 2 treated with the dose of 50 and 100 mg/kg/day were reduced significantly compared to the diabetic control group (**Figure 2D**) .

According to **Figure 2F**, the mean HDL-C shows that the lowest HDL-C level was related to the diabetic control group and the highest value was found in the group treated with curcumin dose of 100 mg/kg/day. Curcumin with low dose of 50 mg/kg/day increased HDL-C, but this increase was not significant. These data suggest that curcumin could increase HDL-C levels (**Figure 2E**) .

The results of **Figure 2G** show the maximum amount of MDA in diabetic control group (4.9 ± 0.29 μmol/l) and the least amount in the healthy control group (1.8 ± 0.12 μmol/l). Both doses of curcumin could significantly reduce MDA levels compared to the diabetic control group.

**Table 1.** Comparison (mean ± SD) of weight and biochemical parameters in four groups.

| Variables/groups | Healthy control | Diabetic control | Curcumin 50 | Curcumin 100 | P-value |
|---|---|---|---|---|---|
| Weight before (kg) | 256.0 ± 10.5 | 270.0 ± 5.8 | 263.0 ± 9.0 | 259.0 ± 9.6 | |
| Weight after (kg) | 272.0 ± 10.5 | 243.0 ± 4.7 | 260.0 ± 12.5 | 268.0 ± 8.2 | |
| Low density lipoprotein cholesterol (mg/dl) | 51.0 ± 4.3 | 67.0 ± 3.8 | 45.5 ± 4.5 | 34.5 ± 4.1 | |
| High density lipoprotein cholesterol (mg/dl) | 36.0 ± 1.9 | 22.5 ± 1.3 | 28.5 ± 0.84 | 36.0 ± 1.7 | |
| Triglyceride (mg/dl) | 5.2 ± 4.4 | 96.2 ± 6.7 | 68.8 ± 4.1 | 69.0 ± 4.2 | |
| Blood glucose (mg/dl) | 124.0 ±5. 7 | 233.0 ± 12.0 | 116.0 ± 8.1 | 134.0 ± 8.7 | |
| Malondialdehyde (μM/l ) | 1.80 ± 0.12 | 4.90 ± 0.29 | 2.88 ± 0.31 | 2.68 ± 0.18 | |

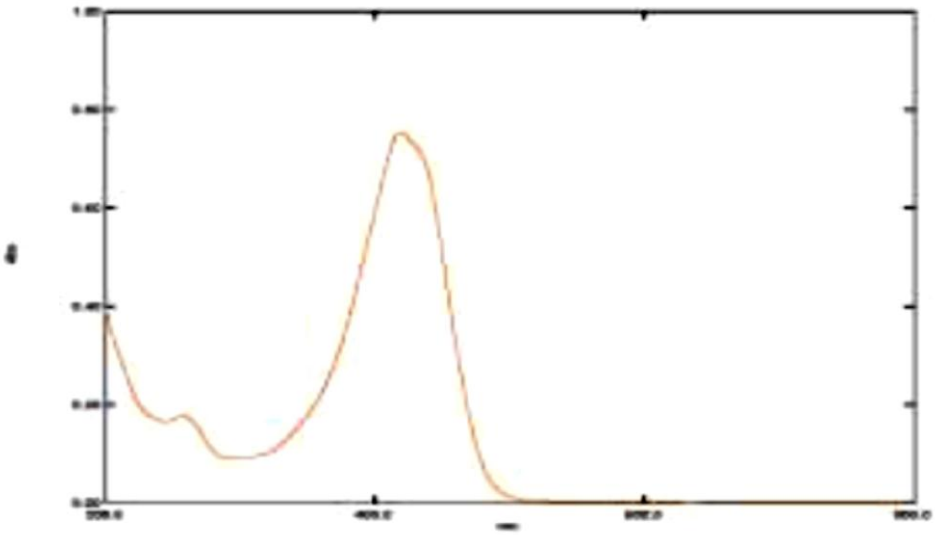
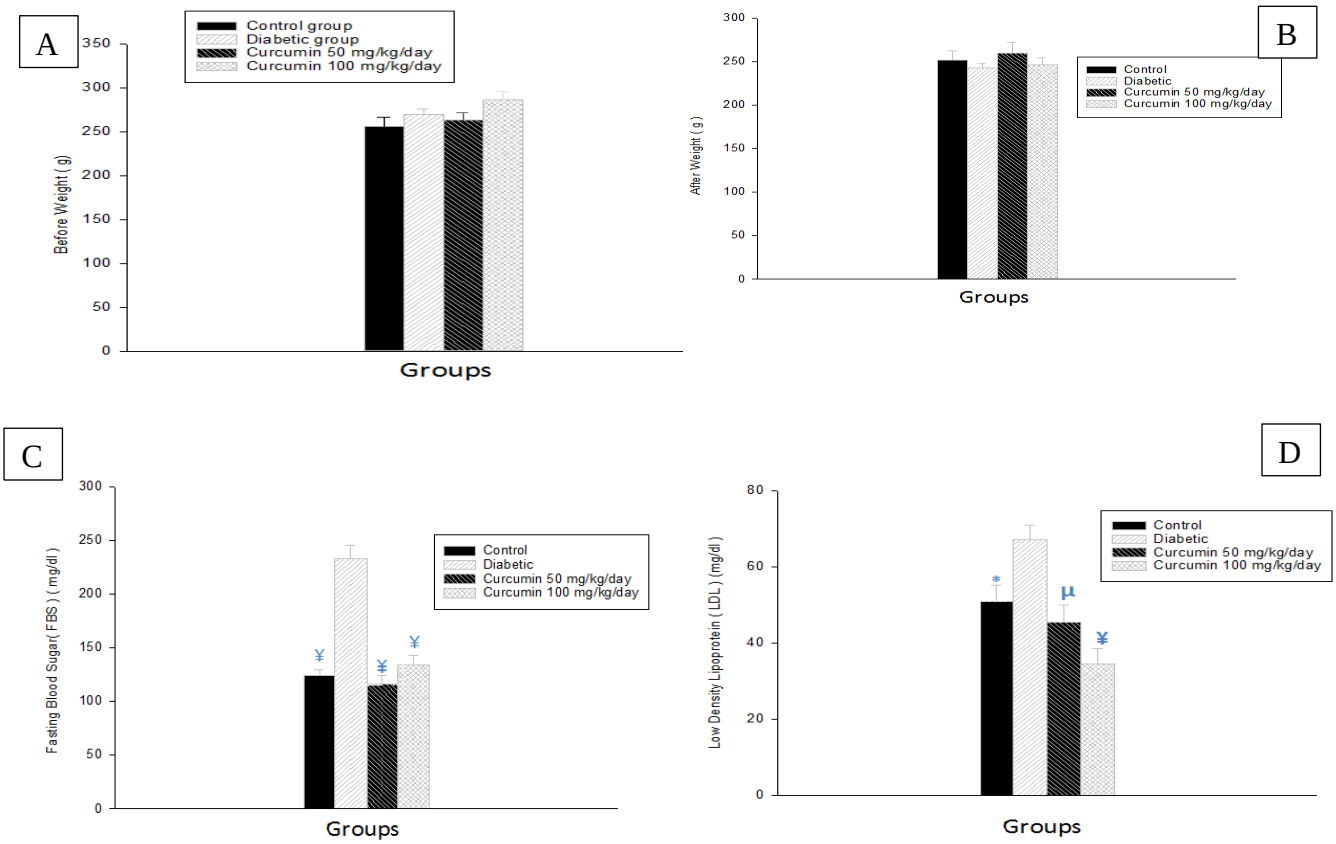


**Figure 1.** UV spectrum of Curcumin



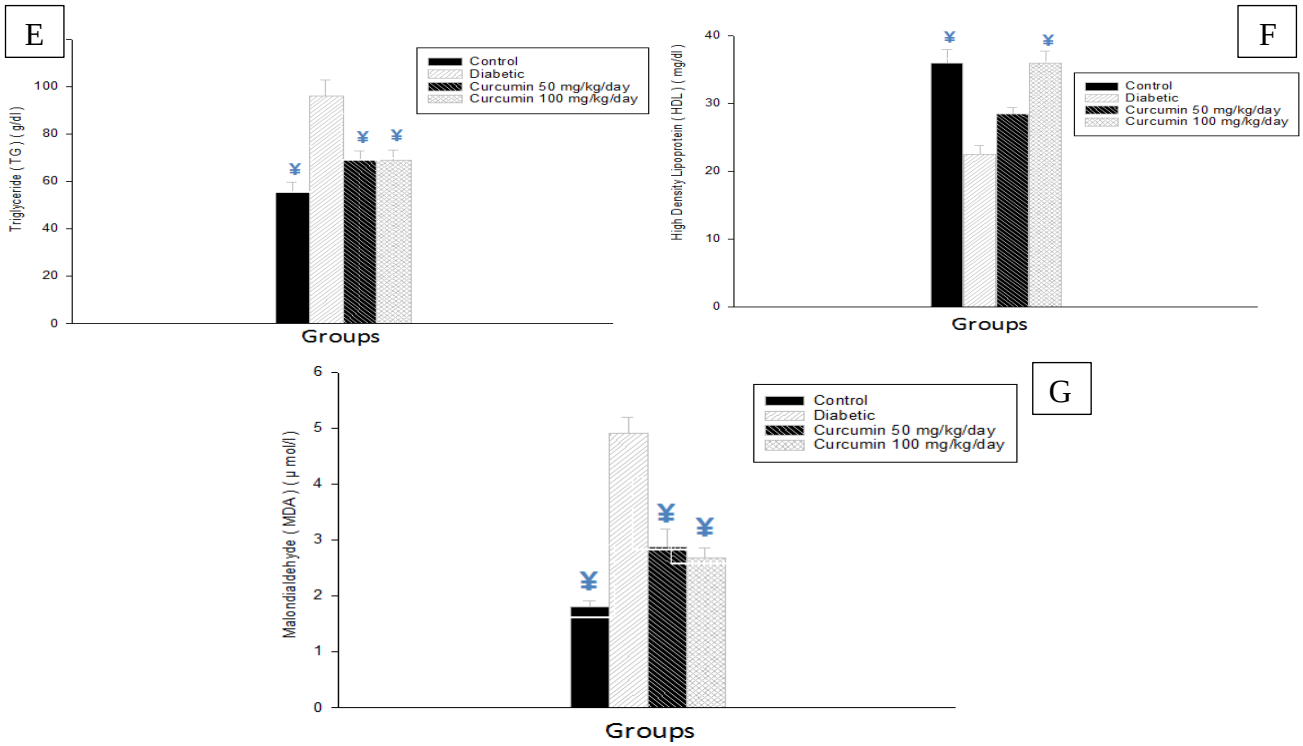



**Figure 2.** Evaluation of anthropometric and biochemical values among studied groups at the end of treatment, as compared to diabetes.

## Discussion

In present study, as shown in **Table 1** and **Figure 2**, dexamethasone injection in diabetic rats increased obviously the blood glucose levels. At the end of the period, curcumin could alter blood glucose levels; so, this was not significantly different from the amount of glucose in healthy control group. Kuhad et al. and Kuroda et al. demonstrated that the curcumin decreased insulin resistance and glucose tolerance, which ultimately reduced blood sugar in dexamethasone-induced diabetes (Kuhad and Chopra, 2007, Kuroda *et al.*, 2005). The results of the present study are consistent with the findings of these researchers. Curcumin reduced the production of inflammatory cytokines and decreased insulin resistance and glucose levels consequently (Maradana *et al.*, 2013, Sajithlal *et al.*, 1998). According to the findings of present study, curcumin may reduced blood glucose levels in diabetic rats by increasing either the pancreatic secretion of insulin, released from insulin bonds as well as enhancing insulin receptor sensitivity (Seo *et al.*, 2008). Previous studies indicated that the dexamethasone-induced diabetes decreased body weight (Shpilberg *et al.*, 2012). In present study, injection of dexamethasone resulted in the weight loss of animals, but the differnce was not significant (**Table 1** and **Figure 2C**). Weight loss in diabetic control group was due to the lack of fat storage because of insulin resistance (Martínez *et al.*, 2016).

In the present study, it curcumin could largely prevent weight loss caused by dexamethasone and curcumin inhibited insulin resistance. Curcumin also increased lipid synthesize and fat storage. As aresult, weight gain increased in the treated groups by activating the enzyme lipoprotein lipase and inhibiting enzyme hormone-sensitive lipase.

In dexamethasone-induced diabetic rats, increase blood glucose levels could enhance the levels of LDL-C and serum TG but decreased HDL-C (Hazra *et al.*, 2008). Hormone sensitive lipase (HSL), as natural intercellular lipase has the ability to hydrolyze TG, cholesterol esters, and other lipids (Sekiya *et al.*, 2009). HSL increases

the level of free fatty acids, transfers them to the liver, and improves the release of TG from the liver. Insulin is known as anti-lipolytic factor and decreases serun TG by reducing the activity of HSL and inhibiting its phosphorylation. Furthermore, insulin increases lipoprotein lipase activity (LPL) on the surface of fat cells, which encourages the entry of fatty acids into the adipose tissue and fat storage (Nishino *et al.*, 2007, Szkudelski and Szkudelska, 2002). Administration of dexamethasone (when the existing insulin resistance reduces LPL activity) decreases TG uptake from TG-rich lipoprotein and ultimately increases TG levels in serum. Direct relationship was reported between the serum LPL activity and HDL-C (Tsutsumi, 2003). In the present study, similar changes were observed in the diabetic control group. Increased TG and LDL-C as well as decreased HDL-C were found in the diabetic control group than the other groups (**Table 1**). Omayma AR et al. showed that curcumin could lead to lower triglyceride and LDL-C levels and increase HDL-C (Omayma *et al.*, 2016). These findings are consistent with the results of the other studies (Omayma *et al.*, 2016, Pari and Murugan, 2007).Curcumin may reduce the serum lipids by inhibiting enzymes involved in lipid synthesis in the liver or improving oxidative stress conditions. Curcumin can decrease HSL activity probably by increasing insulin sensitivity and thus reduces the serum lipids in rats. In general, favorable effects of curcumin on lipid profile can be attributed to the increase in the lipolysis cycle (Belhan *et al.*, 2020).

In patients with diabetes, free fatty acid causes the release of oxygen free radicals, resulting in oxidative stress (McGarry, 2002). Given the reduced antioxidant defense in diabetics, increased production of free radicals may lead to cell dysfunction and oxidative damage to the membrane and increase sensitivity to lipid peroxidation (Ceriello *et al.*, 1991). In this study, symptoms similar to diabetes were observed after administration of dexamethasone in diabetic control group. Following a 30-day course of dexamethasone in the diabetic control group, levels of MDA, as a product of lipid peroxidation, showed a significant increase (**Figure 2G**). In insulin resistance condition, the production of free radicals is increased such as superoxide anion and peroxynitrite (Jansson, 2007). It is known that oxidative stress is both a cause and a consequence of insulin resistance in diabetes (Calles-Escandon and Cipolla, 2001). Curcumin is a strong antioxidant that can reduce insulin resistance and thereby slows down the disease process of diabetes. It should be noted that the increase in serum TG and insulin resistance may lead to enhance expression of IL-1, IL-6, and TNF (Kim *et al.*, 2007). A part of the observed effect of curcumin is probably due to its anti-inflammatory effect (Jurenka, 2009).

Curcumin has an inhibitory effect on Wnt/ JNK1 signaling pathway, which may suppress apoptosis and inflammation (Zhou *et al.*, 2020). Vitali et al. concluded that curcumin decreased proinflammatory cytokines including: TNF-α and IL-6 in vaginal and cervical tissues (Vitali *et al.*, 2020). Therefore, curcumin can be considered as a compound with dual antioxidant and anti-inflammatory effects that improve diabetic complications.

## Conclusion

In summary, curcumin with antioxidant properties had a significant effect on the improvement of metabolic complications ( FBS, LDL-C, TG and HDL-C ) in diabetic rats at the two different doses. These findings can introduce the curcumin as a good candidate for diabetes treatment, especially DM2, which begins with insulin resistance

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## Authors' Contributions

Pourmahmoudi A developed the study idea and theory, participated in drafting the manuscript. Sharif Talebianpoor M supervised the project, participated in drafting the manuscripte, performed

the analysis the data. Vafaiee Nejad T contributed in sample preparation. Mozafari M contributed in sample preparation. Hosseinikia M participated in drafting the manuscript. All authors read the manuscript and verified it.

## Conflict of interest

none declared

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