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Effect of hesperidin treatment on α-Klotho/FGF-23 pathway in rats with experimentally-induced diabetes

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ABSTRACT

Objective Non-alcoholic fatty liver disease, steatohepatitis and nephropathy are considered among the most important complications of diabetes mellitus (DM), which recently increased due to increased frequency of DM and the prolonged life span of diabetic patients The aim of the present study was to reveal the possible effect of hesperidin (HP) on alpha-klotho (α-KL)/ fibroblast growth factor-23 (FGF-23) pathway in rats with diabetes induced by streptozotocin (STZ).

Materials and methods Thirty six male Sprague-Dawley rats were randomly divided into three groups. The rats of the control, diabetes, and treatment groups were fed with standard feed and water throughout the 2-week study. In order to induce diabetes mellitus in rats, those in the diabetes group were administered a single dose of 50 mg/kg STZ. For the DM + HP group, a single dose of 50 mg/kg STZ, when diabetes was induced, hesperidin was administered orally at a dose of 100 mg/kg by gavage.

Results The α-KL levels of our study groups, both the liver and kidney α-KL levels and serum α-KL of the STZ-induced diabetic group were statistically significantly lower than the control group (respectively, $p < 0.05$, $p < 0.001$, $p < 0.05$). It was observed that hesperidin administration statistically significantly increased α-KL levels in serum, liver and renal tissue ($p < 0.001$). Liver, kidney and serum FGF-23 levels of the diabetic group increased significantly in comparison to the control group (respectively, $p < 0.05$, $p < 0.01$, $p < 0.001$). FGF-23 levels that increased in kidney tissue and serum samples of the diabetic group decreased statistically significantly with hesperidin administration (respectively, $p < 0.01$, $p < 0.001$).

Conclusion The α-KL/FGF-23 pathway is a promising bio-indicator in various cases of systemic toxicity and pathology. In addition, the strong positive effects of hesperidin administration on diabetic toxicity in the liver and kidneys suggest that it may be included in the alternative treatment methods in the future.

1. Introduction

Today, chronic diseases with high mortality and morbidity are increasing rapidly worldwide due to sedentary lifestyle and adopting high glycemic index foods. Diabetes mellitus (DM), characterized by hyperglycemia resulting from absolute or relative deficiency of insulin secretion due to pancreatic β-cell dysfunction or insulin resistance, is a chronic disease that affects quality of life and life span negatively due to micro and macro complications [1,2].

In diabetes, protein glycation and glucose autoxidation cause increased formation of free radicals. Lipid peroxidation in membranes is one of the most important mechanisms in cell damage due to free radicals. Structural and functional cell damage occur in the membranes as a result of lipid peroxidation. The unsaturated bonds of cholesterol and fatty acids in the membrane, react with free radicals to form peroxidation. Membrane damage caused by lipid peroxidation is irreversible and has quite harmful consequences [3]. Malondialdehyde (MDA), one of the end products of lipid peroxidation, can cause mutual cross-linking and polymerisation of membrane components. And this causes membrane deformation, and creates changes in the membrane properties such as ion transport, enzyme activity and aggregation of cell surface components. The relationship between diabetic complications and lipid peroxidation was revealed in many studies. For this reason, control of lipid peroxidation is very important [4].

Today researchers focus on identifying molecules that play a role in the pathogenesis of diabetes, which is a common health problem worldwide, having adverse effects on all tissues and organ systems, and causing increased mortality and morbidity rates. A group of researchers

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studying on aging mechanisms have identified a new anti-aging protein and named it Klotho. Klotho protein is expressed in multiple tissues and organs. It was reported that signs of early aging would appear in case of a mutation or dysfunction in alpha-Klotho (α-KL) protein, and the experimental mice were found to be short-lived when expression of KL was inhibited [5,6]. Recent studies have identified numerous functions of the α-KL protein [7]. α-KL protein has important biological functions in bone and mineral metabolism and plays a role as a cofactor in fibroblast growth factor-23 (FGF-23) signalling mechanism. In the literature, α-KL protein was reported to have functions in vitamin D metabolism, calcium and phosphate homeostasis, and maintain endothelial permeability and integrity, and protect against pathological processes such as cancer, vascular calcification and renal fibrosis [8,9]. Increased dietary ingestion of phosphorus increases expression of KL gene. KL leads to enhanced calcium reabsorption by inhibiting endocytosis in renal distal tubules and blocking phosphorus/calcium channels and also causes phosphaturia by blocking reabsorption of phosphate [10]. It is also reported in the literature that the α-KL protein, which is important for the calcium balance in the kidneys, is protective against the oxidative stress [11,12]. The role of the α-KL protein in diabetes mellitus and diabetic nephropathy attracted the attention of researchers in recent years, yet there are not enough studies conducted on this topic. α-KL protein forms a complex with FGF-23 receptor, and it is a mediator for the tasks of FGF-23 [13].

FGF-23 is a recently discovered novel marker candidate. It is released from osteoblasts and osteocytes and consists of 251 amino acids. FGF-23 is secreted to maintain normal phosphorous homeostasis, secondary to dietary oral phosphate intake [14]. FGF-23 molecule was shown to have a role in glucose metabolism as well, in addition to its primary role in phosphate metabolism. Results of a few studies evaluating the effect of FGF-23 on the process of insulin resistance were found to be different from each other [15,16]. According to Wojcik et al., FGF-23 showed a positive effect on insulin sensitivity in individuals with mild insulin resistance but, as an adverse effect, resistance developed against increasing levels of the molecule in those with complicated diabetes and intense inflammation and it could not create the same effect [17].

Diabetes mellitus is a real burden for the patients, causing labour loss and high treatment costs. It is well known that early diagnosis and treatment of diabetes is very important to delay or prevent the onset of diabetic complications. Natural products that are less toxic than synthetic compounds contain a wide variety of active compounds having different pharmacological effects, that are considered more reliable and less expensive [18,19]. Hesperidin (HP), a member of the flavonoid group, is a potent antioxidant found mostly in citrus fruits. It was reported that HP, which is known to have positive effects on inflammation, hypercholesterolemia, and hyperglisemia, can show these effects via inhibition of reactive oxygen radicals [20,21].

Nonetheless, the mechanisms through which HP exhibits its positive effects on diabetes and its relationship with diabetic complications are not clear yet. For this reason, HP which attracted attention in recent years and its effects on liver and kidney will be investigated by taking advantage of streptozotocin (STZ)-induced experimental diabetes model, and α-KL/FGF-23 pathway and lipid peroxidation will be evaluated in this study.

2. Materials and methods

2.1. Chemicals

HP and STZ were purchased from Sigma Chemicals (Sigma Chemicals Co., St. Louis, MO, USA), stored at 2 °C – 4 °C and protected from sunlight. All other chemicals were of analytical grade and were obtained from standard commercial supplies.

2.2. Experimental animals and study groups

A total of 36 healthy adult male Sprague Dawley rats (6–8 wks old, weighing 200–250 g) were obtained from Experimental Animal Research Institute, Erzurum, Turkey. The experimental protocol was approved by the Ethics Committee of Ataturk University. The rats were kept in specially prepared chambers with 19–21 °C constant temperature and 12 h of light/dark periods during the study. While the animals were fed with standard feed, the water needs were provided from the tap water. All animals were provided free access to food and water. Our study groups consisted of 3 groups, namely the control group, diabetes group and diabetes + hesperidin group. The rats of the control, diabetes, and treatment groups were fed with standard feed and water throughout the 2-week study. 0.1 M citrate phosphate buffer was intraperitoneally injected to the control group.

In order to induce diabetes mellitus in rats, those in the diabetes group were administered a single dose of 50 mg/kg STZ, dissolved in 0.1 M citrate phosphate buffer, intraperitoneally [22]. For the DM + HP group, a single dose of 50 mg/kg STZ, dissolved in 0.1 M citrate phosphate buffer was administered intraperitoneally, when diabetes was induced, hesperidin was administered orally at a dose of 100 mg/kg by gavage [23]. Three days after STZ injection, blood samples obtained from rat tail veins were tested for fasting glucose using a glucose meter, and the rats with blood glucose levels above 250 mg/dl were considered diabetic. At the end of a 2-week study period, following 12 h of fasting, abdominal and thoracic cavities of the rats were dissected under general anesthesia using ketamine-xylazine combination and liver and kidney tissue samples were taken in addition to blood samples (Figs. 1–3).

Blood samples for glucose, aspartate aminotransferase (AST), alanin aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, α-KL, FGF-23 and MDA levels were taken to tubes containing no anticoagulant at room temperature and centrifuged at 4000 x g for 10 min at + 4 °C and sera were stored at − 20 °C until analyzed. Liver and kidney tissue specimens extracted were washed three times with cold (4 °C) 0.9% sodium chloride and fractionated. Liver and kidney tissues were stored at − 80 °C until analyzed. Measurements of α-KL, FGF-23 and MDA were analyzed in liver and kidney tissues.

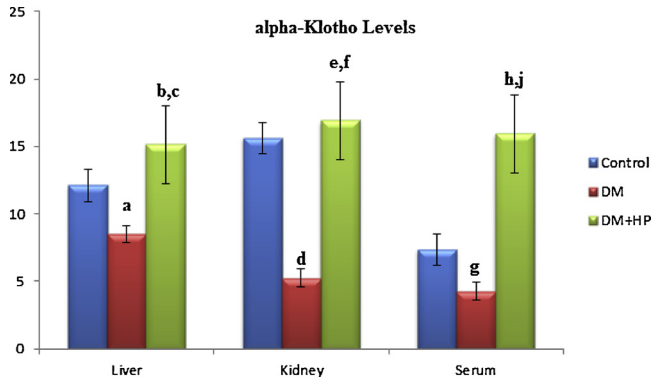

Fig. 1. Effect of hesperidin on serum, liver and kidney α-Klotho levels in rats with diabetes.
[a]Significantly different when compared with control group, ($p < 0.05$).
[b]Significantly different when compared with DM group, ($p < 0.001$).
[c]Significantly different when compared with control group, ($p > 0.05$).
[d]Significantly different when compared with control group, ($p < 0.001$).
[e]Significantly different when compared with DM group, ($p < 0.001$).
[f]Significantly different when compared with control group, ($p > 0.05$).
[g]Significantly different when compared with control group, ($p < 0.05$).
[h]Significantly different when compared with DM group, ($p < 0.001$).
jSignificantly different when compared with control group, ($p < 0.001$).

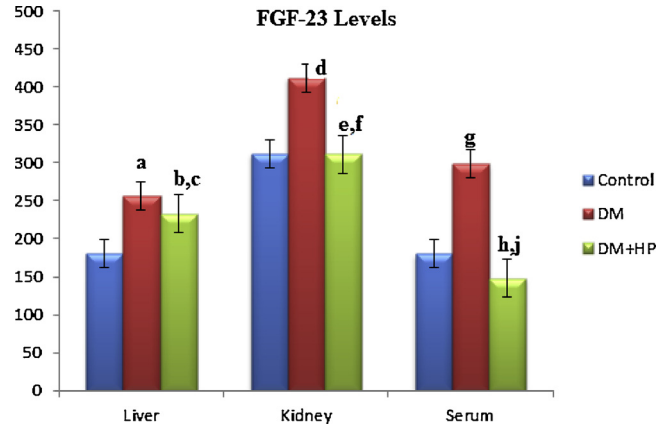

Fig. 2. Effect of hesperidin on serum, liver and kidney FGF-23 levels in rats with diabetes.
[a]Significantly different when compared with control group, ($p < 0.05$).
[b]Significantly different when compared with DM group, ($p > 0.05$).
[c]Significantly different when compared with control group, ($p < 0.05$).
[d]Significantly different when compared with control group, ($p < 0.01$).
[e] Significantly different when compared with DM group, ($p < 0.01$).
[f]Significantly different when compared with control group, ($p > 0.05$).
[g] Significantly different when compared with control group, ($p < 0.001$).
[h]Significantly different when compared with DM group, ($p < 0.001$).
*j*Significantly different when compared with control group, ($p > 0.05$).
DM: diabetes mellitus; HP: hesperidin; FGF-23: fibroblast growth factor-23.

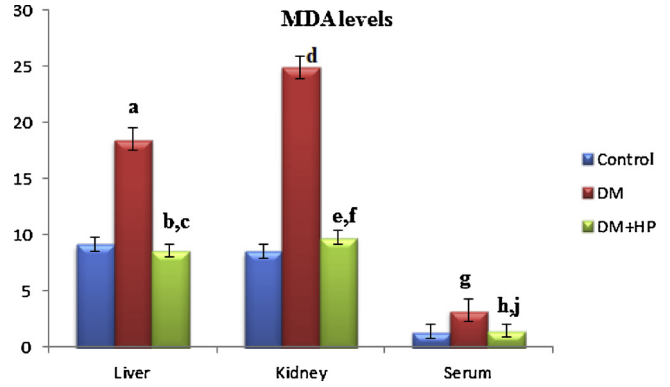

Fig. 3. Effect of hesperidin on serum, liver and kidney MDA levels in rats with diabetes.
[a]Significantly different when compared with control group, ($p < 0.001$).
[b]Significantly different when compared with DM group, ($p < 0.001$).
[c]Significantly different when compared with control group, ($p > 0.05$).
[d]Significantly different when compared with control group, ($p < 0.001$).
[e]Significantly different when compared with DM group, ($p < 0.001$).
[f]Significantly different when compared with control group, ($p > 0.05$).
[g]Significantly different when compared with control group, ($p < 0.05$).
[h]Significantly different when compared with DM group, ($p < 0.05$).
*j*Significantly different when compared with control group, ($p > 0.05$).
DM: diabetes mellitus; HP: hesperidin; MDA: malondialdehyde.

2.3. Biochemical analyzes

Liver and kidney tissues kept deep frozen were thawed and homogenized with 1/10 cold 0.1 M phosphate buffer (pH: 7.4) using a homogenizer. Tissue homogenates were centrifuged at 4000 x g for 20 min at 4 °C to obtain supernatants. α-KL and FGF-23 levels were determined in samples of liver and kidney tissues. The serum and tissue α-klotho (SunRed Biological Technology, Co., Ltd. Shanghai) and FGF-23 (SunRed Biological Technology, Co., Ltd. Shanghai) levels were measured by means of Enzyme Linked Immunosorbent Assay (ELISA) technique, using Rat ELISA kit with the test procedure recommended by the producer. The tissue α-KL results were expressed as ng/mg protein and tissue FGF-23 results were expressed as pg/mg protein. The serum α-KL results were expressed as ng/ml and serum FGF-23 results were expressed as pg/ml.

Lipid peroxidation in serum and tissue samples was measured spectrophotometrically by the method of Ohkawa et al [24]. This method is based on the reaction of MDA, one of the aldehyde products of lipid peroxidation, with thiobarbituric acid (TBA). The resulting MDA forms a pink complex with TBA, and the extent of lipid peroxidation is determined by spectrophotometric measurement of the absorbance of this solution at 532 nm. The total protein levels in the liver and kidney samples were determined in accordance with the Biuret method [25].

Table 1
Serum biochemical parameters of the groups.

	Control	DM	DM + HP
Glucose (mg/dL)	128,00 ± 7,00	420,00 ± 30,50[a]	205,00 ± 15,00[b,e]
AST (U/L)	24,00 ± 9,50	96,00 ± 23,34[a]	34,00 ± 12,50[b,d]
ALT (U/L)	30,45 ± 5,25	165,35 ± 20,25[a]	55,15 ± 15,00[b,e]
BUN (mg/dL)	15,20 ± 2,10	48,15 ± 7,15[a]	19,35 ± 5,15[c,d]
Creatinin (mg/dL)	0.50 ± 0,08	2,64 ± 0,12[a]	0.90 ± 0,04[c,d]

Data were given as mean ± SD.
AST : Aspartate aminotransferase, ALT : Alanine aminotransferase, BUN: Blood Urea Nitrogen, DM: Diabetes mellitus, HP: Hesperidin.
[a] Significantly different when compared with control group, ($p < 0.001$).
[b] Significantly different when compared with DM group, ($p < 0.001$).
[c] Significantly different when compared with DM group, ($p < 0.05$).
[d] Significantly different when compared with control group, ($p > 0.05$).
[e] Significantly different when compared with control group, ($p < 0.05$).

3. Results

The serum glucose, AST, ALT, BUN and creatinine results in our study are presented in Table 1. Serum glucose, AST, ALT, BUN and creatinine values in the experimental diabetes group were statistically significantly increased in comparison to the control group ($p < 0.001$). Administration of HP however, was observed to reduce serum glucose, AST, ALT, BUN and creatinine levels statistically significantly with respect to the diabetic group (respectively, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.05$, $p < 0.05$). Serum glucose and ALT values in the DM + HP group were statistically significantly increased in comparison to the control group ($p < 0.05$) but there were no statistically significant differences in the AST, BUN and creatinine parameters between the control and DM + HP groups ($p > 0.05$). When we compare the α-KL levels of our study groups, both the liver (8.51 ± 0.45) and kidney (5.23 ± 0.12) α-KL levels and serum (4.25 ± 0.65) α-KL levels of the STZ-induced diabetic group were statistically significantly lower than the control group (respectively, $p < 0.05$, $p < 0.001$, $p < 0.05$). It was observed that HP administration statistically significantly increased α-KL levels in liver (15.15 ± 1.95), renal tissue (16.90 ± 1.67) and serum (15.92 ± 2.17) ($p < 0.001$). Serum α-KL (15.92 ± 2.17) values in the DM + HP group were statistically significantly increased in comparison to the control group (7.34 ± 1.44) ($p < 0.001$) but there were no statistically significant differences in the liver (15.15 ± 1.95) and kidney (16.89 ± 1.67) α-KL values between the control (12.10 ± 1.17, 15.63 ± 1.15) and DM + HP groups ($p > 0.05$).

Liver (256.63 ± 18.14), kidney (412.41 ± 17.69) and serum (298.07 ± 19.34) FGF-23 levels of the diabetic group increased significantly in comparison to the control group (respectively, 180.68 ± 18.41, 312.28 ± 21.83, 180.34 ± 21.45) (respectively, $p < 0.05$, $p < 0.05$, $p < 0.001$). FGF-23 levels that increased in kidney tissue and serum samples of the diabetic group decreased statistically significantly with HP administration (respectively, $p < 0.01$, $p < 0.001$). Liver FGF-23 level was not changed with HP

administration ($p > 0.05$). Liver FGF-23 (232.98 ± 26.32) values in the DM + HP group were statistically significantly increased in comparison to the control group (180.68 ± 18.41) ($p < 0.05$) but there were no statistically significant differences in the serum and kidney FGF-23 values between the control and DM + HP groups ($p > 0.05$). In our study, liver (18.49 ± 1.23), kidney (24.91 ± 1.71) and serum (3.25 ± 0.89) MDA levels in the diabetic group increased statistically significantly when compared with respect to the control group (respectively, 9.16 ± 0.65, 8.52 ± 0.96, 1.36 ± 0.21) (respectively, $p < 0.001$, $p < 0.001$, $p < 0.05$). HP however, decreased MDA levels of liver and kidney tissues as well as serum MDA levels, statistically significantly with respect to the diabetic group (respectively, $p < 0.001$, $p < 0.001$, $p < 0.05$). There were no statistically significant differences in the serum, liver and kidney MDA values between the control and DM + HP groups ($p > 0.05$).

4. Discussion

Our current study shows that STZ-induced diabetes could be recovered by HP treatment. As indicated by the results of this study, we understand that diabetes-induced hepatotoxicity and nephrotoxicity in rats can be categorized in relation to the disturbances in blood parameter levels, in particular the parameters indicating liver and kidney functions like AST, ALT, BUN, and creatinine levels. According to the World Health Organization (WHO) data in 2001, there are 171 million DM patients worldwide [26]. It is anticipated that the number of diabetic patients worldwide will reach 285 million in 2010 and will increase to 439 million by 2030 [27]. Non-alcoholic fatty liver disease, steatohepatitis and nephropathy are considered among the most important complications of diabetes mellitus, which recently increased due to increased frequency of DM and the prolonged life span of diabetic patients [28].

For this reason, AST, ALT, BUN and creatinine levels have an important place in the follow up of liver and kidney functions of diabetic patients. In the diabetic group, a significant increase was determined in transaminase levels that are liver enzymes, as sell as in BUN and creatinine levels, which are measured in order to evaluate kidney function levels. A significant decrease was observed in AST, ALT, BUN and creatinine levels in the diabetic group treated with HP treatment. Li et al. reported that HP treatment decreased blood glucose levels by positively affecting increased glucose levels [29]. In our study too, HP treatment was found to significantly decrease blood glucose levels. Cirrhosis is one of the causes of mortality in diabetic patients. Lipid accumulation in hepatocytes and oxidative stress due to reactive oxygen radicals increase the incidence of hepatocellular carcinoma in diabetic patients. Oxidative stress leads to DNA damage and cell death [30,31]. In our study, serum, liver and kidney MDA levels of the diabetes group were significantly higher than the control group. Lipid peroxidation plays an important role in the development of diabetes-related complications. In the literature, an increase in MDA levels increases free radical-induced tissue damage, which leads to pancreatic β-cell dysfunction. Lipid peroxidation inhibits the use of glucose in peripheral tissues by reducing insulin secretion [32,33]. Having determined in their study on diabetic nephropathy that the level of MDA, the end product of lipid peroxides, was significantly higher in the diabetic group, Elmas et al. suggested that the increase in lipid peroxidation may be an important criteria for the development of diabetes and related complications [34].

Based on our previous studies as well as the other studies in the literature, we can also say that lipid peroxidation and the accompanying oxidative stress are important in the pathogenesis of diabetes. Although numerous medicines are developed and used for the treatment of diabetes, due to their toxicity, particularly in the liver and kidneys, as well as their failure to respond patients' expectations, as a matter of fact alternative therapies in diabetes become even more important [35]. In our study, we observed that hesperidin treatment inhibited lipid peroxidation by reducing MDA levels in liver, kidney and serum. Hesperidin treatment was reported to inhibit lipid peroxidation by increasing total antioxidant capacity, also in a study by Homayouni et al. [36] evaluating oxidative DNA damage and lipid peroxidation in diabetic patients.

There are few studies on the effect of α-KL on liver and kidney in diabetes mellitus. α-Klotho plays a key role in the control of mineral and vitamin D metabolisms and is required for the binding of FGF-23 as an FGF receptor [37]. Although the studies mainly focused on the effects of serum α-KL protein on calcium and phosphate metabolism, there is also evidence that it plays a role in suppressing oxidative stress due to its effects on insulin metabolism [38,39]. In their study with diabetic patients, Nie et al. [40] found significantly lower α-KL levels in diabetics than in healthy controls, and suggested that such a decrease in α-KL levels could be involved in the pathological mechanism of diabetes. In another study on diabetic nephropathic patients, Kim et al. [41] suggested that plasma α-KL levels may be used as an early predictor of renal failure in diabetic patients. In our study too, serum, liver and kidney α-KL levels of diabetes group were found significantly lower than control group. In parallel with that, a significant increase was observed in α-KL levels of the hesperidin treated group. Yamamoto et al. [12] reported protective effects of klotho protein against oxidative stress, noting its anti-aging function by inhibiting insulin/insulin-like growth factor-1 (IGF-1) signaling pathway. Although vitamin D is an important regulator in the synthesis of klotho protein, other factors inducing synthesis are not completely identified [42].

FGF-23 is known to be associated with phosphate uptake in the kidney. Mutations in the FGF-23 gene lead to increased levels of serum FGF-23, hypophosphatemia and defects in bone mineralization [43]. In the literature, klotho protein was reported to function as an obligatory co-receptor for FGF-23 [9]. In our study, FGF-23 levels were significantly higher in the serum, liver and kidney tissue samples of the diabetic group with respect to the control group. In the literature, increased levels of FGF-23 were reported in the patients with type-2 diabetes and concomitant non-alcoholic fatty liver [44]. Another study on alcoholics highlighted that increased levels of FGF-23 were associated with hepatic dysfunction, diabetes, hypertension and obesity [45]. KL deficiency causes the rate of glomerular filtration decrease, in both acute renal failure and chronic renal disease; while excessive KL maintains this rate. It was reported that α-KL measurement may be a better predictor of renal functions than FGF-23 in terms of reflecting functional nephron mass [46,47]. Because α-KL levels decrease in parallel to the development of progressive renal dysfunction, much earlier than the elevation of FGF-23 levels. Development of extra-renal complications in acute and chronic renal damage can be avoided and progression can be delayed by correcting α-klotho deficiency [48,49].

In our study, hesperidin administration in the diabetes group reversed the picture of decreased α-KL and increased FGF-23 levels. Hesperidin, having an antioxidant effect, removed disorders in the axis of α-KL/ FGF-23, increased α-KL levels in serum, liver and kidney, and decreased FGF-23 and MDA levels. It is obvious that every new finding, having the significance as an early diagnostic marker, can be critical for diagnosis, follow-up and treatment of the patients. For this purpose, optimal biomarkers are needed for maintaining health, early diagnosis, evaluation of treatment efficacy and prognosis. The α-KL/FGF-23 pathway is a promising bio-indicator in various cases of systemic toxicity and pathology. In addition, the strong positive effects of HP administration on diabetic toxicity in the liver and kidneys suggest that it may be included in the alternative treatment methods in the future.

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Conflict of interest

The authors declared no conflicts of interest.

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