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Determination of the effects of Chia (*Salvia hispanica L.*) oil and dandelion (*Taraxacum Officinale*) extract on tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) release in liver tissue of diabetic rats

Şükran Yediel Aras [1] Pınar Aksu Kiliçle [2] Sevda Eliş Yildiz [1] Erhan Uluman [2] Buket Bakir [3] Ebru Karadağ Sari [4] Serpil Dağ [5]

[1] *Department of Midwifery, Faculty of Health Sciences, Kafkas University, Kars, Türkiye.*
[2] *Department of Biology, Faculty of Arts and Sciences, Kafkas University, Kars, Türkiye.*
[3] *Department of Histology and Embryology, Faculty of Veterinary Medicine, Namık Kemal University, Tekirdağ, Türkiye.*
[4] *Department of Histology and Embryology, Faculty of Veterinary Medicine, Kafkas University, Kars, Türkiye.*
[5] *Department of Pathology, Faculty of Veterinary Medicine, Kafkas University, Kars, Türkiye.*

Correspondence: *Şükran Yediel Aras (s.yediel@hotmail.com)*
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ABSTRACT

Objective: This study aimed to investigate the effects of Chia (*Salvia hispanica L.*) oil and Dandelion (*Taraxacum Officinale*) extract on Tumor Necrosis Factor-α (TNF-α) and Interleukin 6 (IL-6) release in liver tissue of diabetic rats.

Materials and Methods: Experimental groups were created as control, sham, chia, dandelion, diabetes (DM), diabetes+chia (DC), and diabetes+dandelion (DD). Body weight and blood glucose measurements were taken on the 1st, 3rd, and 17th days of the study and evaluated statistically. A one-way ANOVA test was performed to determine the differences between the groups. The Duncan test was used to compare significant differences between groups. At the end of the study, Masson's trichrome staining and Hematoxylin-Eosin staining were employed for histological examinations of liver tissues, and the distribution of TNF-α and IL-6 was examined by applying the Streptavidin-biotin peroxidase method.

Results: It was determined that body weight and blood glucose measurements were significantly decrease for the DC group compared to other groups. Immunoreactivity of TNF-α and IL-6 was found to decrease in DC and DD groups at close to the control levels.

Conclusion: Based on our results, it was thought that the use of chia and dandelion in diabetes may contribute to the alleviation of disease-related complications by having a positive effect on proinflammatory cytokine levels.

Keywords: *Chia, Dandelion, Diabetes mellitus, IL-6, TNF-α*

INTRODUCTION

Diabetes is a chronic disease characterized by the absence of insulin production (Type 1 diabetes) or the development of insulin resistance (Type 2 diabetes and gestational diabetes) (WHO, 1999). The most common causes of diabetes are hereditary and environmental causes. The most obvious symptom of this disease is that blood glucose levels are higher than normal (Tierney et al., 2002). The World Health Organization (WHO) reported that there were approximately 422 million diabetics worldwide in 2014. It has been noted that most of the increase in the number of diabetes patients is in developing low- and middle-income countries. WHO data of 2016 show that diabetes ranks fourth in deaths due to 'non-infectious diseases' with a death rate of 1.6 million. It has been reported that diabetes directly caused 1.5 million deaths in 2019 (WHO, 2020; WHO, 2021).

Cytokines are soluble proteins or glycoproteins that regulate the relationships of immune system cells with each other in both the natural and specific immune response (Köklüdağ, 1999; Manuel et al., 1999). Cytokines have been reported to play a role in the development of many chronic complications, including neurological and vascular lesions, in patients with diabetes (Shanmugam et al., 2003). Tumor necrosis factor-alpha (TNF-α), one of the cytokines, is a protein released from alveolar macrophages, monocytes, neutrophils, and lymphocytes (Martinet et al., 1988; Sung et al., 1988; Djeu et al., 1990). Interleukin-6 (IL-6), on the other hand, is a cytokine released by monocytes, alveolar macrophages, endothelial cells, fibroblasts, B and T cells (Kotloff et al., 1990; Zitnik et al., 1993).

Chia is an annual herbaceous plant from the mint family (*Labiatae*). Chia, a plant that grows annually in an area extending from western Mexico to northern Guatemala, grows in the temperature range of 15-30 degrees and needs a high amount of precipitation. Chia use has been reported to have positive effects in cases such as weight loss, obesity, and diabetes (Ayerza and Mealla, 1993; Vuksan et al., 2017). Dandelion is a plant in the genus *Taraxacum* and is a member of the *Asteraceae* family. It has been used as a medicinal plant for many years. Dandelion use is beneficial in relieving type 2 diabetes, blisters, spleen, and liver complaints (Alarcon-Aguilara et al., 1998; Honek et al., 2011).

It is known that cytokines such as TNF-α and IL-6 are associated with the development of complications in patients with diabetes. It is also suggested that chia and dandelion plants may have a positive effect on diabetes. Therefore, the view that alternative treatments can be developed in the treatment of diabetes and its complications forms the basis of this study. This study aims to reveal the effects of Chia (*Salvia hispanica L.*) oil and Dandelion (*Taraxacum Officinale*) extract on the liver tissue of rats with experimental diabetes and on TNF-α and IL-6, which are pro-inflammatory cytokines, by immunohistochemical methods.

MATERIALS and METHODS

Ethical approval was obtained from the Animal Experiments Local Ethics Committee of Kafkas University for the study (Project No: KAU HADYEK/2019-027). The animals used in the study were obtained from the Experimental Animals Unit of Kafkas University.

Materials

This study was designed as a future-oriented experimental study. Forty-nine 3-month-old *Spraque dawley* male rats were used in the study. Rats were housed in standard cages at an ambient temperature of 22±2°C, 12 hours of light, 12 hours of dark environment, and fed as *ad-libitum*. The study was carried out following the principles of the International Declaration of Helsinki. All rats were weighed before experimental rats were grouped. Experimental groups were created from randomly selected rats so that each group had 7 rats.

Methods

Experimental rats were grouped as follows:

1. Control group (n:7): No application was made to rats in this group. They were fed only rat feed.
2. Sham group (n:7): A single dose of sodium citrate solution 50 mg/kg intraperitoneal (i.p.) was administered to rats in this group.
3. Chia Group (n:7): Chia oil (naturaoil, barcode no: 8-697589-643265) was administered as 1ml/ kg by oral gavage for 14 days to rats in this group (Baş et al., 2016).
4. Dandelion Group (n:7): 2.4 g/kg dandelion extract (Kale natural herbal products, serial no: LE 487) was administered to rats in this group by oral gavage for 14 days (Cho et al., 2002).
5. Diabetes group (DM) (n:7): The rats in this group were administered a single dose of streptozotocin (STZ) (50 mL citric acid+40 mL disodium was dissolved in hydrogen phosphate buffer solution and set to pH: 4.5) 50 mg/kg i.p., and rats with a blood glucose value of 200 mg/dL were considered diabetic.
6. Diabetes+Chia Group (DC) (n:7): A single dose of streptozotocin (STZ) (50 mL citric acid + 40 ml disodium hydrogen phosphate was dissolved in buffer solution and set to pH: 4.5) 50 mg/kg i.p. was administered to the rats in this group and diabetes was created. Then 1 mL/kg chia oil was administered by oral gavage for 14 days.

7. Diabetes+Dandelion Group (DD) (n:7): The rats in this group were administered a single dose of streptozotocin (STZ) (50 mL citric acid+40 mL disodium hydrogen phosphate was dissolved in buffer solution and set to pH: 4.5) 50 mg/kg i.p. and diabetes was created. Then the dandelion extract was applied as 2.4 g/kg through oral gavage for 14 days.

At the end of the study, liver tissues were taken from the rats under deep anesthesia and fixed in a 10% solution of formalin for histological and immunohistochemical examinations. It was then blocked in paraffin by undergoing routine histological tissue follow-up procedures.

Body Weight Measurement

The weights of all rats were measured on the first day of the study, 72 hours after STZ administration, and after 8 hours of fasting at the end of the experiment.

Determination of Blood Glucose Levels

To determine fasting blood glucose levels, blood samples were taken from the tail vein of rats before starting the STZ administration and after 72 hours starving period following STZ administration and after 8 hours of fasting at the end of the study and measured with a glucometer (Yasee, GLM-76, Taiwan).

Histological Investigations

Masson's trichrome staining technique and Hematoxylin-Eosin staining were performed to examine the general structure of liver tissue in the sections taken from paraffin blocks.

Immunohistochemistry

Slides in which tissue sections were taken were coated with chromium-alum gelatin, and the Streptavidin-biotin peroxidase method was applied to the sections. PBS (0.1 M, pH, 7.2) buffer was used for all washing operations during the immunohistochemical procedure. The sections were incubated for 15 minutes at 3% H_2O_2 prepared at 0.1 m PBS and boiled in citrate buffer solution at 800 watts in a microwave oven for 10 minutes. It was then incubated for 10 min with a Large Volume Ultra V Block solution. TNF-α (Santa Cruz-sc52746) primary antibody (1/500 dilution) and IL-6 (Biorbty-orb651448) primary antibody (1/200 dilution) were applied to the sections at room temperature and in a humid environment for 1 hour. After that, Biotinylated Goat Anti B Polyvalent solution and Streptavidin Peroxidase solution were applied at room temperature for 30 minutes. DAB-H_2O_2 (Diaminobenzidine-Hydrogen Peroxide) Substrate solution was added for chromogen application. Modified Gill III hematoxylin solution was used for contrast staining. All procedures were performed exactly without adding primary antibodies to the sections held in PBS to determine whether immunoreactivity was specific. For immunohistochemical assessment, staining properties and density of target cells were taken into account. The assessment was carried out by two independent observers. Semi-quantitative scoring was made from 0 to 3 based on no reaction (0), weak reaction (1), moderate reaction (2), strong reaction (3). All prepared sections were evaluated and photographed under a light microscope (Olympus BX51, Olympus Optical Co. Osaka, Japan).

Statistical Analysis

SPSS (20.0) packaged software was used to evaluate the data obtained in the study. A one-way ANOVA test was performed to determine the differences between the groups. The Duncan test was used to compare significant differences between groups. The results were expressed as mean ± standard deviation (SD). Also, a p-value <0.05 was considered statistically significant.

RESULTS

Body Weight Results

According to the body weight measurement days (1, 3, and 17 days), there was no statistically significant difference in the comparison made within the groups ($p>0.05$) (Table 1). A statistically significant difference was found in the comparison between the groups at 1, 3, and 17 days ($p<0.05$) (Table 2, Figure 1). Especially, in the 17-day DC group, it was noted that the weights decreased significantly compared to other groups.

Fasting Blood Glucose Results

A fasting blood glucose assessment was performed on days 1, 3, and 17. It was found that there was a statistically significant difference in the comparison made within the groups in these days ($p<0.05$) (Table 3). Especially, on the 3rd day of the study, it was determined that fasting blood sugar values increased in DM, DC, DD groups. Fasting blood glucose values were compared between groups on days 1, 3, and 17; there was a statistically significant difference in DM, DC, DD groups on day 3, and DM and DD groups on day 17 ($p<0.05$) (Table 4, Figure 2).

Table 1. Evaluation of body weights within the groups.

Days	Control (gr)	Sham (gr)	DM (gr)	Chia (gr)	DC (gr)	Dandelion (gr)	DD (gr)
1st day	257.71±45.04	258.42±21.85	276±34.45	285.57±18,33	230±25.35	280.57±52.95	282±42.22
3rd day	264.28±42.75	264.71±22.10	280.71±42.84	292.57±20,31	214.57±26.04	296.85±48.35	290.14±32.52
17th day	271.71±45.40	272.28±40.38	296.57±40.31	304.85±23,91	207.14±56.81	32757±42.90	265.14±15.39
p	0.842	0.683	0.6	0.246	0.545	0.208	0.351

Table 2. Evaluation of body weights between the groups.

Days	Control (gr)	Sham (gr)	DM (gr)	Chia (gr)	DC (gr)	Dandelion (gr)	DD (gr)	p
1st day	257.71±45.04^{a}	258.42±21.85^{a}	276±34.45^{b}	285.57±18.33^{b}	230±25.35^{a}	280.57±52.95^{b}	282±42.22^{b}	0.07
3rd day	264.28±42.75^{a}	264.71±22.10^{a}	280.71±42.84^{a}	292.57±20.31^{a}	214.57±26.04^{b}	296.85±48.35^{a}	290.14±32.52^{a}	0.001
17th day	271.71±45.40^{a}	272.28±40.38^{a}	296.57±40.31^{ac}	304.85±23.91^{ac}	207.14±56.81^{b}	327.57±42.90^{c}	265.14±15.39^{a}	0.000

a, b, c: There is a statistically significant difference between the means shown with different letters on the same line (p<0.05).

Table 3. Evaluation of fasting blood glucose measurements within the groups.

Days	Control (mg/dl)	Sham (mg/dl)	DM (mg/dl)	Chia (mg/dl)	DC (mg/dl)	Dandelion (mg/dl)	DD (mg/dl)
1st day	77.43±6.80	77.86±3.98	79.86±6.26	84.57±11.16	87.86±13.01	77.29±2.98	83.14±5.49
3rd day	96.57±14.06^{b}	96.43±4.86^{b}	406.57±109.07^{b}	95.71±12.63^{a}	300.57±78.02^{b}	78.29±2.50^{a}	465.14±54.91^{b}
17th day	83.71±10.81^{a}	95±8.16^{b}	320.86±76.43^{b}	78.28±6.18^{b}	135.43±28.51^{a}	86.43±13.14^{a}	256.29±80.37^{c}
p	0.01	0.000	0.000	0.018	0.000	0.086	0.000

a, b, c: There is a statistically significant difference between the means indicated by different letters in the same column (p<0.05).

Table 4. Evaluation of fasting blood glucose measurements between the groups.

Days	Control (mg/dl)	Sham (mg/dl)	DM (mg/dl)	Chia (mg/dl)	DC (mg/dl)	Dandelion (mg/dl)	DD (mg/dl)	p
1st day	77.43±6.80^{a}	77.86±3.98^{a}	79.86±6.26^{a}	84.57±11.16^{a}	87.86±13.01^{a}	77.29±2.98^{a}	83.14±5.49^{a}	0.1
3rd day	96,.57±14.06^{a}	96,.43±4.86^{a}	406.57±109.07^{b}	95.71±12.63^{a}	300.57±78.02^{c}	78.29±2.50^{a}	465.14±54.91^{b}	0.000
17th day	83.71±10.81^{a}	95±8.16^{ab}	320.86±76.43^{c}	78.28±6.18^{a}	135.43±28.51^{b}	86.43±13.14^{ab}	256.29±80.37^{d}	0.000

a, b, c: There is a statistically significant difference between the means shown with different letters on the same line (p<0.05).

Histopathological Results

No pathological findings were found in the liver tissue of rats in the control, sham, chia, and dandelion group (Figure 3). In addition to sinusoidal dilation and hyperemia in liver tissue of DM group rats, necrosis in hepatocytes was observed in some areas, also DC and DD groups had lower necrotic changes in hepatocytes compared to the DM group (Figure 4).

Immunohistochemical Results

TNF-α Immunoreactivity

TNF-α immunoreactivity were determined around the central veins in the liver tissue of rats a weak in control, sham, chia, dandelion groups; strong in the DM group, and moderate in DC and DD groups (Figure 5).

IL-6 Immunoreactivity

IL-6 immunoreactivity was no detected in the control, sham, chia and dandelion groups. Strong IL-6 immunoreactivity in the DM group and moderate in the DC and DD groups were determined around the central veins (Figure 6).

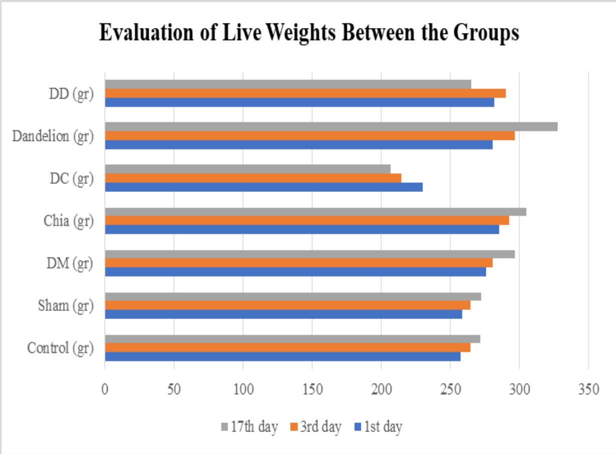

Figure 1. Evaluation of live weights between the groups.

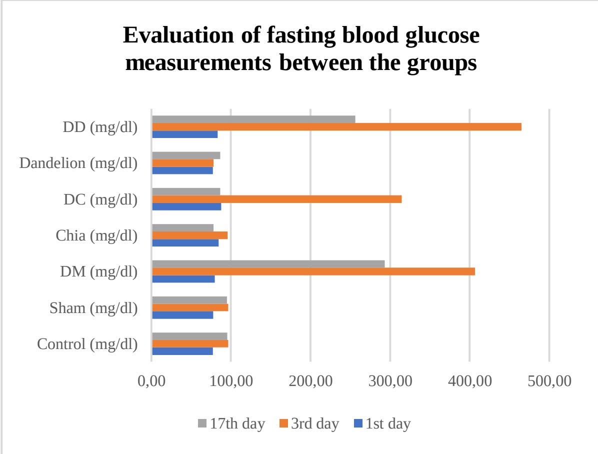

Figure 2. Evaluation of fasting blood glucose measurements between the groups.

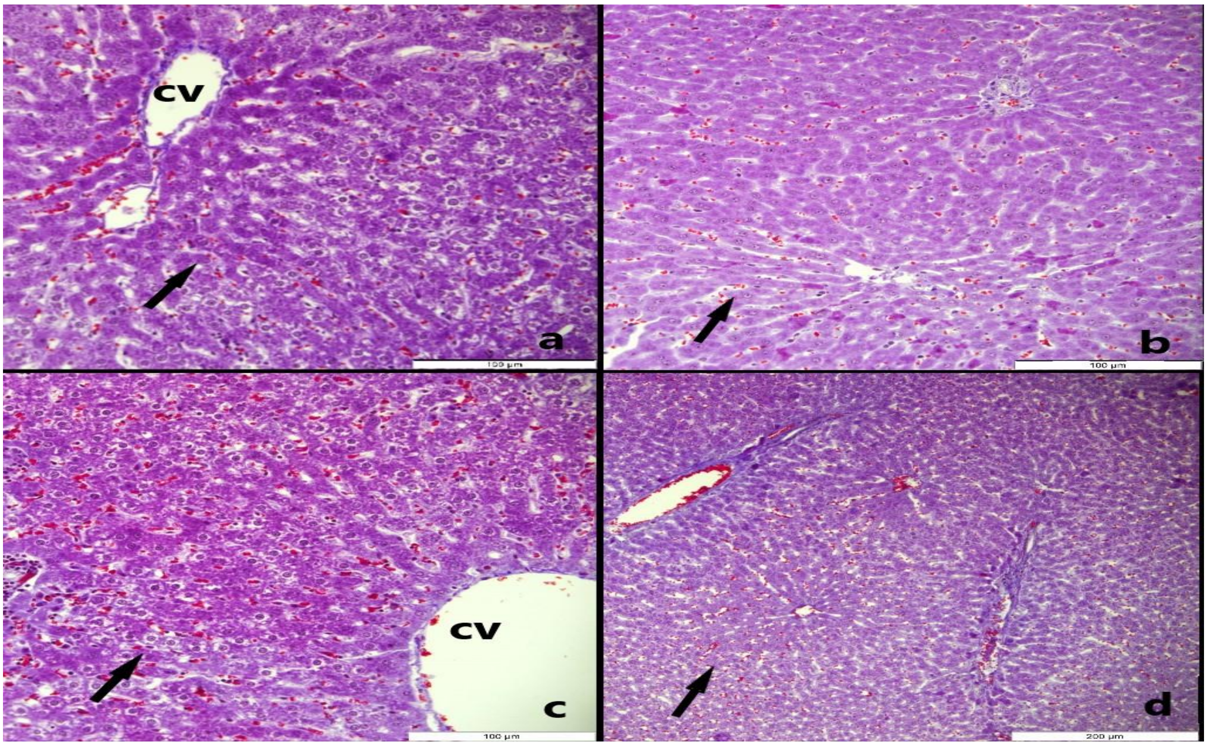

Figure 3. Rat liver tissue. a: Control, b: Sham, c: Chia, d: Dandelion. cv: Central vein, arrow: Hepatocytes. Masson's trichrome staining.

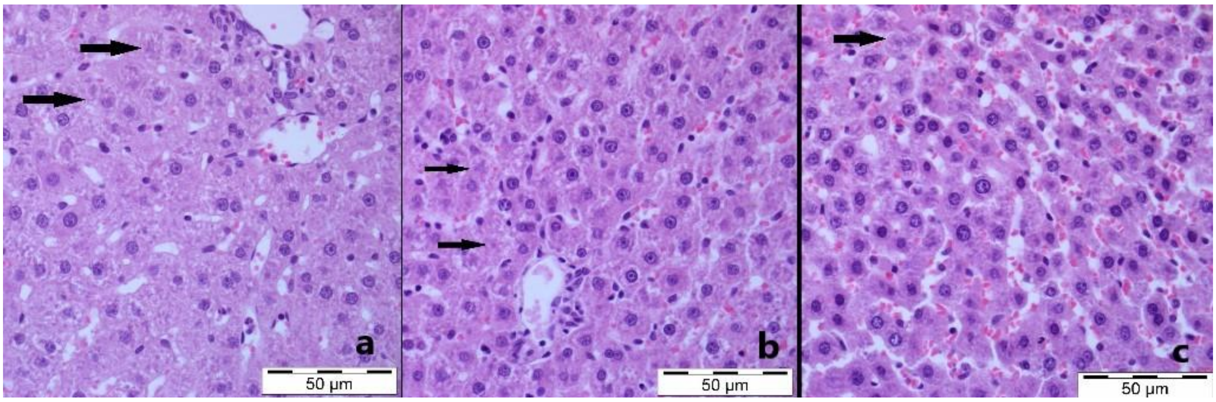

Figure 4. Rat liver tissue. a: Diabetes, b: DC, c: DD. Necrotic changes in hepatocytes (arrows). Hematoxylin-Eosin staining.

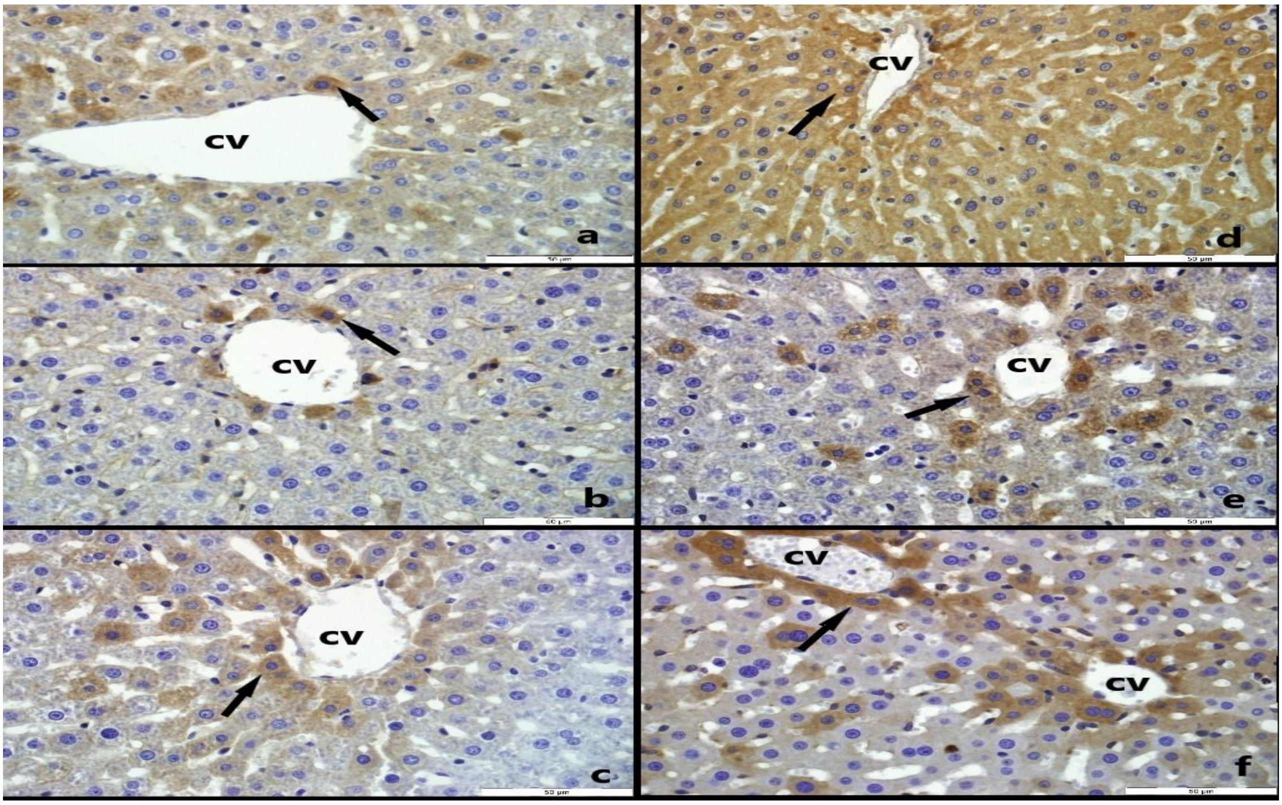

Figure 5. TNF-α immunoreactivity in rat liver tissue. a: Control, b: Chia, c: Dandelion, d: Diabetes, e: DC, f: DD. cv: Central vein, arrow: Hepatocytes. Bar: 50μm.

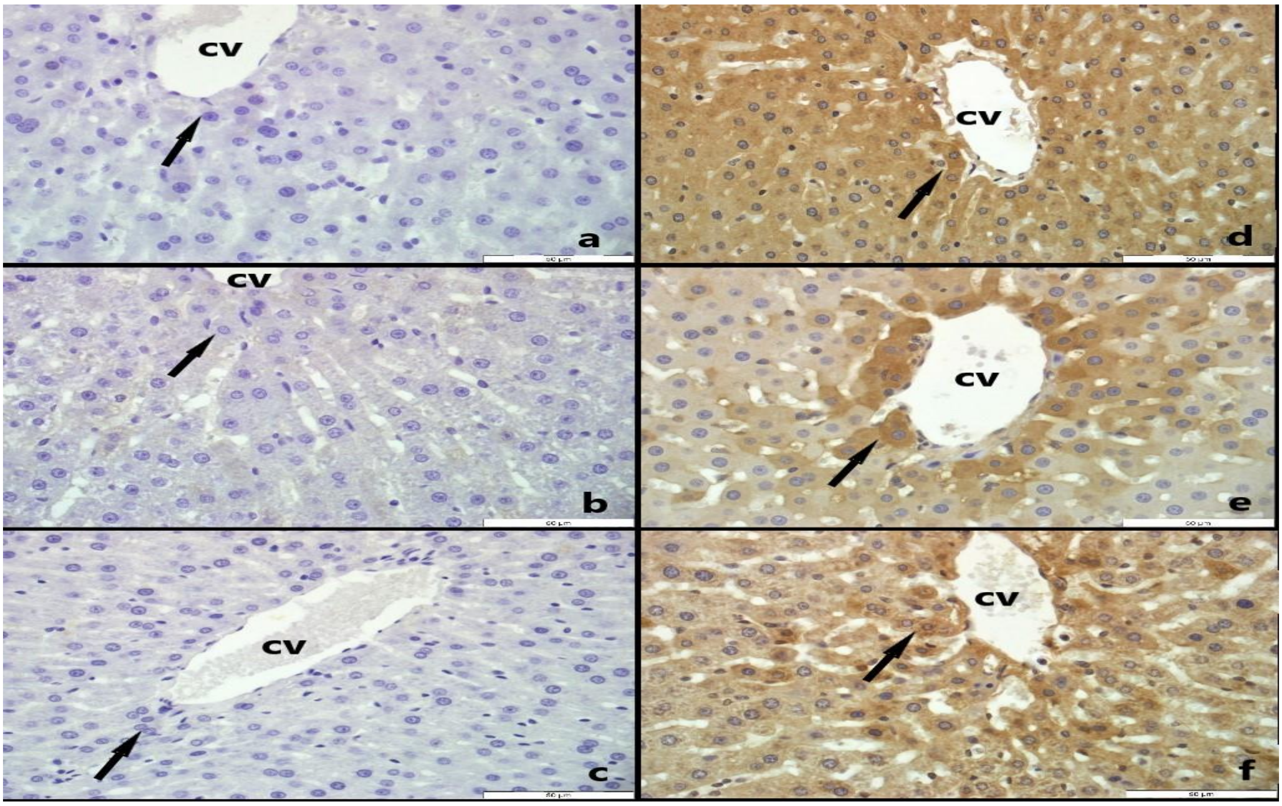

Figure 6. IL-6 immunoreactivity in rat liver tissue. a: Control, b: Chia, c: Dandelion, d: Diabetes, e: DC, f: DD. cv: Central vein, arrow: Hepatocytes. Bar: 50μm.

DISCUSSION

Chia has been reported to have positive effects on decreasing body weight, serum triglycerides, and high blood sugar values, and increasing high-density lipoprotein levels (Ayerza and Coates, 2007; Guevara-Cruz et al., 2012). Long-term use of chia seeds in the diet has been shown to increase bone mineral content, as well as reduce lipid accumulation in the liver, and have a positive effect on intestinal muscle layers and crypt size morphology (Chani et al., 2018). A study conducted on obese rats found that consumption of chia seeds and chia oil did not reduce body weight increase and abdominal fat accumulation, but only improved glucose and insulin tolerance (Marineli et al., 2015a). It has been reported that dandelion administration in diabetic rats reduces cholesterol, triglycerides, malondialdehyde, blood glucose levels, and body weight levels, and increases serum HDL-cholesterol levels. Due to the mentioned characteristics, it has been suggested that dandelion may have positive effects on diabetes (Cho et al., 2002). At the end of the study, it was determined that body weight measurements and blood glucose levels significantly decreased especially in the DC group compared to rats in the DM and DD group. There was no significant difference between DM and DD groups in terms of body weight measurements and blood glucose levels. Our results suggested that Chia administration would have a positive effect, in particular, on controlling high blood sugar levels. In addition, we concluded that the duration of dandelion extract application may have different effects on the results.

Structural and functional disorders occur in the liver due to diabetes, and therefore glycogen and lipid metabolism is influenced (Levinthal and Tavill, 1999; Sanchez et al., 2000). As a result of diabetes, oxidative stress increases in many organs, especially the liver, also, bloating in hepatocytes, chromatin condensation, apoptotic bodies, and necrosis occur (Tolman et al., 2007; Manna et al., 2010). In rats with STZ-induced diabetes, degeneration and necrosis in hepatocytes in liver tissue, inflammatory cell infiltration in portal areas, fibrosis, and bile duct hyperplasia were observed (Yaman and Doğan, 2016). It has been suggested that the use of chia has positive effects on liver tissue in diseases such as non-alcoholic dyslipidemia, non-alcoholic steatohepatitis, and hepatocellular carcinoma (Fernandez-Martinez et al., 2019). The use of chia has been stated to have a positive effect on preventing and normalizing dyslipidemia and hepatic steatosis. In addition, rats fed a high-fat diet containing chia seeds had a decrease in thiol, plasma catalase, and glutathione peroxidase levels, and an increase in liver glutathione reductase levels (Rossi et al., 2013; Marineli et al., 2015b). Dandelion has been reported to significantly inhibit lipid accumulation in the liver, reduce insulin resistance, and have positive effects in the prevention and treatment of non-alcoholic fatty liver disease (Davaatseren et al., 2013). In our study, sinusoidal dilation and hyperemia, as well as necrosis of hepatocytes in some areas, were observed in liver tissue of DM group rats. DC and DD group hepatocytes indicated lower levels of necrotic changes compared to DM group hepatocytes. Considering the changes observed in our study and the information in the literature, our results suggest that the use of chia and dandelion may be protective against damage to the liver caused by diabetes.

As a result of oxidative stress, the amount of ROS (reactive oxygen species) increases, and insulin resistance develops with the secretion of cytokines in high amounts from activated macrophages and monocytes. In Type 2 diabetes mellitus, insulin resistance increases along with inflammation associated with oxidative stress and activation of monocytes, and insulin secretion decreases due to the destruction of pancreatic island cells (Navarro-Gonzales and Mora-Fernandez, 2008; Elmarakby and Sullivan, 2012). Tumor necrosis factor-α is a proinflammatory cytokine34 released from myeloid cells as a result of activation of the MAPK (mitogen-activated protein kinase) and NFkB (nuclear factor-kB) signaling pathways. TNF-α is found mainly in human fat (adipose) tissue. TNF-α and TNF-α mRNA levels in adipose tissue increase in direct proportion to the level of obesity and hyperinsulinemia, and TNF-α levels decrease as a result of a decrease in adipose tissue due to weight loss (Hotamisligil et al., 1995; Kern et al., 1995). In addition, elevated serum TNF-α levels have been reported in patients with type 1 and type 2 diabetes. Because of this effect, it has been noted that TNF-α can be used to control diabetes and evaluate the pro-inflammatory immune response that develops in diabetes (Foss-Freitas et al., 2006). In a study that examined TNF-α expression and immunohistochemical distribution in chronic liver damage, TNF-α positive cells were rarely observed along sinusoids in the control group's hepatic tissue, while immunoreactivity was not observed in hepatocytes (Orfila et al., 1999). A study conducted in diabetic rats indicated moderate immunoreactivity of TNF-α around the central veins in the liver tissue of control group rats, while strong immunoreactivity was reported in the diabetes mellitus group (Satin et al., 2016). In the study, moderate immunoreactivity of TNF-α was detected around the central veins in the control, sham, chia, dandelion groups, and strong immunoreactivity of TNF-α was detected in the DM group. It was also noted that chia and dandelion administration reduced the increased the immunoreactivity of TNF-α in diabetes mellitus.

Interleukin-6 is a proinflammatory cytokine that allows the differentiation of monocytes into macrophages (Chomarat et al., 2000). In addition, IL-6 increases insulin resistance and glucose transport in fat cells. Thanks to this effect, it has been reported that IL-6 may play a role in insulin-stimulated glucose transport (Stouthard et al., 1996; Rotter et al., 2003). When both cytokine levels were evaluated together in diabetic rats, hepatic steatosis and degree of inflammation, serum TNF-α and IL-6 levels, hepatic TNF-α and IL-6 mRNA expression, immunoreactivity of TNF-α in liver tissue were significantly higher than in the control group (Zhang et al., 2009; Li et al., 2018). The determination that immunoreactivity of TNF-α and IL-6 was strong in the DM group and moderate in DC and DD groups suggests that chia and dandelion use may have positive effects on increased proinflammatory cytokine levels in diabetes.

CONCLUSION

The frequency of diabetes-related complications and its high death rates around the world also increases the importance of treating this disease. Natural-origin treatment methods for chronic diseases such as diabetes in developed and developing countries are gaining popularity due to fewer side effects. Many traditional medicines are made of medicinal plants, minerals, and organic substances. Therefore, chia and dandelion plants are also considered to be effective in the treatment of many diseases today. It is emphasized that some cytokines, such as TNF-α and IL-6, are effective in the proinflammatory response and may have positive effects on certain diseases that occur in the liver. In our study, we determined that Chia use was especially effective in lowering high blood glucose, while chia and dandelion administration reduced TNF-α and IL-6 immunoreactivity in liver tissue in rats with diabetes. When our histopathological, immunohistochemical, and statistical results are evaluated together, we concluded that the use of chia and dandelion can have a positive effect on TNF-α and IL-6 levels and that these plants, which stimulate the pro-inflammatory response, can be used as a natural source of treatment for diabetes.

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Author's Contributions: ŞYA designed, collected, analyzed and interpreted experiments prepared the data and the article. ŞYA, PAK, SEY and EU performed the experiment. EKS designed the experiments, oversaw the project, and critically read the paper. SD performed histopathological examinations. All authors approved the final version of the published article.

ŞYA:Şükran Yediel Aras, PAK:Pınar Aksu Kiliçle, SEY:Sevda Eliş Yildiz, EU:Erhan Uluman, BB:Buket Bakir, EKS:Ebru Karadağ Sari, SD:Serpil Dağ

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