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Histopathological Evaluation of the Anti-Obesity Effects of the Plant Kenger (*Gundelia tournefortii* L.) in an Experimental Model of Obesity Induced in Rats

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ABSTRACT In this study, the anti-obesity effects of *Gundelia tournefortii* extract were histopathologically investigated in experimental obesity induced by a high-calorie diet in rats. For this purpose, Wistar-Albino male rats were divided into four groups, each consisting of 10 rats: Control (C), High-Calorie Diet (HC), High-Calorie Diet + *Gundelia tournefortii* 200 mg/kg (HCG1), and High-Calorie Diet + *Gundelia tournefortii* 400 mg/kg (HCG2). The study was conducted over a period of three months. Histopathological analyses of liver tissue samples revealed that the HC group exhibited fatty degeneration, with coagulation necrosis observed in hepatocytes. In the HCG1 group, the liver showed macro-microvesicular fat vacuoles in hepatocytes of the pericentral regions, although this accumulation was significantly milder compared to the HC group. Conversely, the HCG2 group displayed a histological appearance close to that of the control group, with only rare microvesicular fat vacuoles in hepatocytes. As a result, it is evaluated that the *Gundelia tournefortii* extract given with a high-calorie diet in rats has a hepatoprotective effect.

Keywords: *Gundelia tournefortii, Histopathology, Obesity.*

ÖZ

Deneysel Obezite Modeli Oluşturulan Ratlarda Kenger (*Gundelia tournefortii* L.) Bitkisinin Antiobezite Etkisinin Histopatolojik Olarak Değerlendirilmesi

Bu çalışmada, yüksek kalorili diyet ile deneysel obezite oluşturulan ratlarda, kenger (*Gundelia tournefortii*) bitki ektresinin antiobezite etkisinin histopatolojik olarak araştırılması amaçlanmıştır. Bu amaçla Wistar-Albino ırkı erkek ratlar, her grupta 10 rat olacak şekilde toplam 4 gruba Kontrol (K), Yüksek Kalorili Diyet (YK), Yüksek Kalorili Diyet + *Gundelia tournefortii* 200mg/kg (YKG1), Yüksek Kalorili Diyet + *Gundelia tournefortii* 400 mg/kg (YKG2) ayrıldı ve çalışma 3 ay süre ile yürütüldü. Elde edilen sonuçlara göre, karaciğerlerden alınan doku örneklerinden yapılan histopatolojik analizler sonucunda; YK grubunda yağlanma ile hepatositlerin bazısında ise koagulasyon nekrozu izlenmiştir. Ayrıca YKG1 grubundaki ratların karaciğerlerinde YK grubunda olduğu gibi lopçukların periasiner bölgelerindeki hepatositlerde makro-mikroveziküler yağ vakuollerinin bulunduğu, ancak bu birikimlerin YK grubuna göre çok daha hafif olduğu gözlenmiştir. Diğer yandan, YKG2 grubunda histolojik görünümün kontrol grubuna yakın olmakla birlikte hepatositlerde çok seyrek olarak mikroveziküler yağ vakuollerinin bulunduğu tespit edilmiştir. Sonuç olarak; ratlarda yüksek kalorili diyet ile birlikte verilen kenger bitki ekstresinin, hepatoprotektif etkisinin olduğu değerlendirilmektedir.

Anahtar Kelimeler: *Gundelia tournefortii, Histopatoloji, Obesite.*

INTRODUCTION

Obesity emerges as a complex disease that threatens both developed and developing countries, affecting all age groups with its social and psychological aspects (WHO 2017). The primary factors leading to obesity are unbalanced nutrition and a lack of physical activity. Moreover, it has been recognized that genetic, biochemical, physiological, psychological, neurological, environmental, and socio-cultural factors also impact the development of obesity (Chakrabarti 2009; Wright and Aronne 2012).

In addition to medical, behavioral, and physical treatments, various interventions such as dietary measures, surgical procedures, acupuncture, and hypnosis are available for obesity management (Yanovski 2011; Apovian et al. 2015; Bautista et al. 2019). With the growing emphasis on ethnopharmacology, the selection of plant species for testing the safety, efficacy, and quality of pharmacological effects against obesity has become an essential scientific tool in both in vivo and in vitro studies (de Freitas and de Almeida 2017). Epidemiological and

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clinical studies have shown that consuming bioactive components, mainlythose rich in secondary metabolites, provides therapeutic properties against obesity-related problems (Mir et al. 2019). It has been suggested that diets rich in active components can be used as an alternative dietary option to suppress oxidative stress and inflammation in the adipose tissues of obese individuals (Mir et al. 2019). Additionally, plant phenols and polyphenols play a role in preventing various pathological conditions due to their antioxidant properties (Losso et al. 2007; Haghi 2011).

The plant *Gundelia tournefortii*, used in this study, has been traditionally favored in medicine. Belonging to the Asteraceae family, it primarily grows in the temperate regions of Asia, including Turkey, Iran, Egypt, Jordan, Cyprus, and Turkmenistan (Çoruh et al. 2007; Matthäus and Özcan 2011). It is particularly rich in phenolic content, including derivatives of caffeoylquinic acid, quercetin gallic acid, and other components responsible for the plant's biological activity (Hajizadeh-Sharafabad et al. 2016; Konak et al. 2017). Additionally, the stalks of this plant are thought to have hepatoprotective properties (Konak et al. 2017). The liver, a significant metabolic organ, plays a crucial role in regulating homeostasis through carbohydrate, protein, and fat metabolism, bile acid production, and drug detoxification (Sapmaz et al. 2015; Koike 2018; Matz-Soja 2019). Therefore, this study aims to histopathologically investigate the effects of *Gundelia tournefortii* (Kenger) plant extract on the development of obesity in rats fed a high-calorie diet.

MATERIAL AND METHODS

The study was conducted with the approval of the Van Yuzuncu Yil University Laboratory Animal Ethics Committee (Date: 31.01.2023, Decision No: 2023/03-15).

Preparation of Plant Material

The plant material used in the study, *Gundelia tournefortii* L., was collected around the province of Van in May. The lyophilized aqueous extract of the plant was prepared according to a modified version of the method by Dalar and Konczak (2013). After the collected plant sample was divided into pieces, 100 grams were weighed and blended with 500 ml of distilled water. The obtained extract was homogenized at +4 °C for 2 hours using a shaker. After homogenization, the mixture was centrifuged for 20 minutes at 10,000 rpm, and the supernatants were separated from the solvent using an evaporator at +37 °C. The concentrated extract was frozen in distilled water, and then lyophilized at -51 °C and 50 millitorr pressure for one week. The obtained lyophilized aqueous fraction was stored at -20 °C until the analysis procedures began.

Experimental Animals

The live subjects used in our research, male Wistar albino rats, were obtained from the Van Yuzuncu Yil University Laboratory Animal Unit. Throughout the experiment, the rats were housed at a temperature of 25±1 °C with a 12-hour light/12-hour dark cycle and were fed ad libitum.

Preparation of Experimental Groups

The rats used in the study were divided into four equal groups. The groups were as follows:

1. Control (C) group: Rats were fed standard rat chow and tap water for three months.

2. High-Calorie Diet (HC) group: Rats were fed a high-calorie rat chow and tap water for three months.

3. High-Calorie Diet + *Gundelia tournefortii* 200 mg/kg (HCG1) group: In addition to the high-calorie rat chow, rats were administered *Gundelia tournefortii* plant extract (200 mg/kg) orally via gavage for the last four weeks.

4. High-Calorie Diet + *Gundelia tournefortii* 400 mg/kg (HCG2) group: In addition to the high-calorie rat chow, rats were administered *Gundelia tournefortii* plant extract (400 mg/kg) orally via gavage for the last four weeks.

All feeds used in the study were obtained from Research Diet. The dosages of the plant extract used in the study (200 and 400 mg/kg) were determined according to the acute toxicity test guidelines of OECD 425 (Organization for Economic Cooperation and Development) (OECD 2008).

Histopathological Examination

At the end of the study, the rats were sacrificed under anesthesia. Liver tissue samples from the rats were fixed for 72 hours in a 10% buffered formaldehyde solution. The tissue samples were then routinely processed and embedded in paraffin blocks. Sections of 4 µm thickness were cut from these blocks using a microtome (Leica RM 2135) and stained using Hematoxylin-Eosin (H.E.) and Oil Red O fat staining techniques. The sections were examined under a light microscope (Nikon80i-DS-RI2).

RESULTS

In the control group, microscopic examination of the rats' livers showed a normal histological appearance. The structure of hepatocytes and portal areas appeared normal, with hepatocytes forming regular remark cords around the central vein, and the sinusoids between these cords were of standardwidth (Fig 1A).

In the (HC) group, a microscopic examination of the rats' livers revealed the presence of macro or microvesicular vacuoles of various sizes with sharp boundaries in the cytoplasm of hepatocytes (Fig 1B-C). Additionally, staining with the special Oil Red O fat stain confirmed these vacuoles contained orange-colored fat deposits (Fig 1D). These morphological changes were localized in the periacinar regions of the lobules. Particularly, coagulation necrosis was observed in many of these hepatocytes. The necrotic hepatocytes typically had darkly stained, pyknotic, and flattened nuclei. Other common microscopic findings included congestion in the central veins and sinusoid dilation. Inflammatory reactions consisting of focal mononuclear cell infiltrations were observed in some portal areas.

In the (HCG1) group, sharp-bordered macro or micro vesicular fat vacuoles were found in hepatocytes of the periacinar regions of lobules (Fig 1E), similar to the HC group. However, these morphological changes were significantly milder compared to the HC group. Moreover, the necrotic changes and congestion in the central veins observed in the HC group were not present in this group. In the (HCG2) group, the histological appearance of all rats' livers was close to that of the control group. However, micro vesicular fat vacuoles were rarely observed in hepatocytes, but neither the necrotic changes in hepatocytes nor congestion in the central veins were detected (Fig 1F).

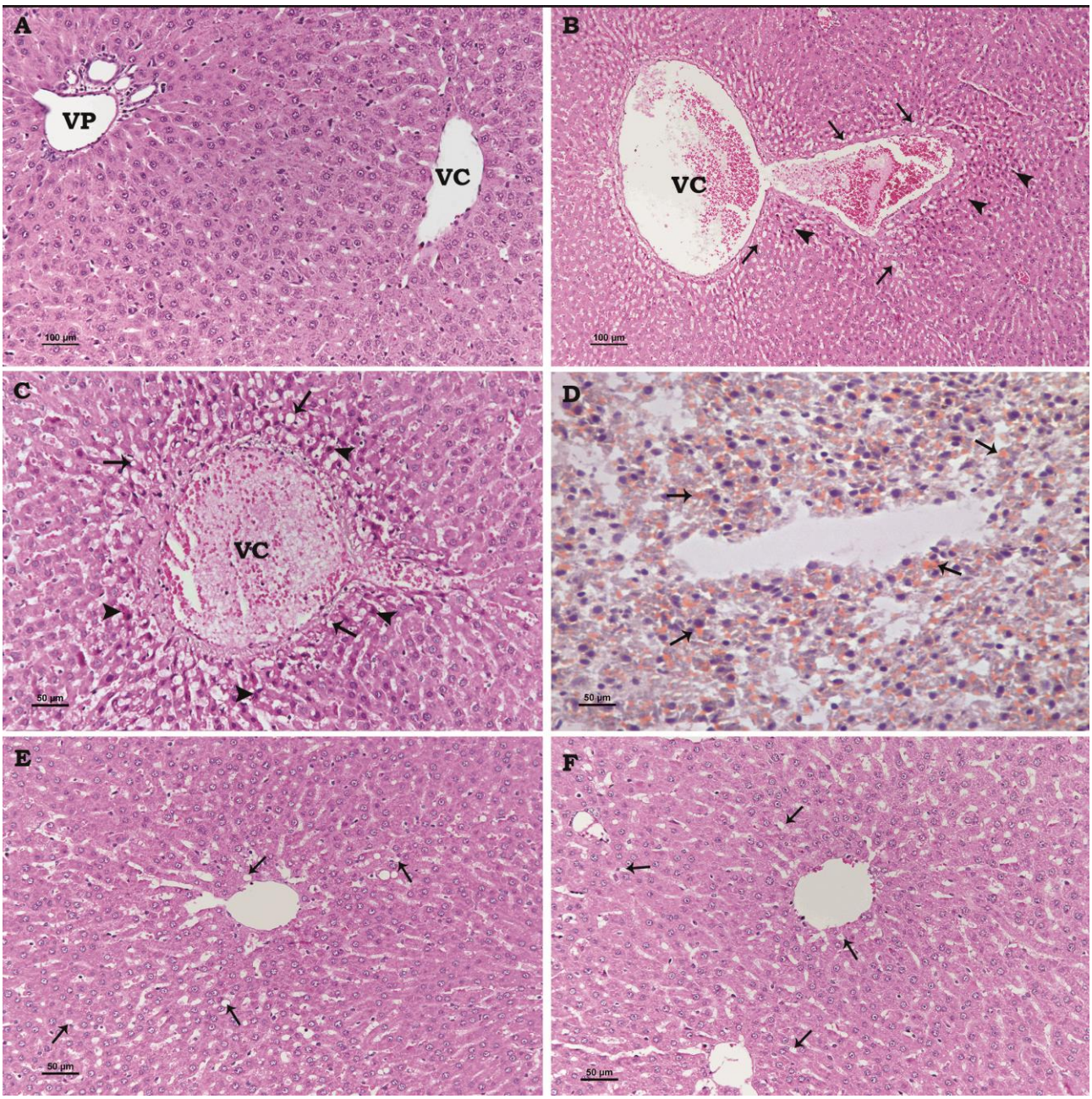

Figure 1: Histopathological images for all groups.

A) C group: The normal microscopic appearance of the liver is observed, with central veins (VC) and portal vein (VP). H.E. Bar; 100 µm. B) HC group: Congestion in central veins (VC) and vacuolar degeneration in centrilobular hepatocytes (arrows) along with coagulation necrosis (arrowheads) are observed in the liver. H.E. Bar; 100 µm. C) HC group: Centrilobular hepatocytes show sharply defined vacuoles of varying sizes (arrows) and coagulation necrosis in hepatocytes (arrowheads). H.E. Bar; 50 µm. D) HC group: Hepatocytes exhibit orange-colored lipid deposits of varying sizes (arrows) in the liver. Oil Red O. Bar; 50 µm. E) HCG1 group: Centrilobular hepatocytes display sharply defined vacuoles (arrows). H.E. Bar; 50 µm. F) HCG2 group: Centrilobular hepatocytes show sharply defined vacuoles (arrows). H.E. Bar; 50 µm.

DISCUSSION AND CONCLUSION

Obesity is recognized globally as a significant public health issue, rapidly increasing in prevalence. It is a major risk factor for the development of many chronic diseases such as heart disease, diabetes, hypertension, certain types of cancer, and musculoskeletal disorders (WHO 2020). According to WHO data, since 1975, the global obesity rate has tripled. In 2016, 39% of adults worldwide aged 18 and over were classified as overweight, and 13% were classified as obese (WHO 2016). Obesity is a multifactorial condition arising from the interaction of genetic, environmental, behavioral, and psychosocial factors. An imbalance between energy intake and expenditure is one of the fundamental causes of obesity. The prevalence of high-calorie, processed foods and a decrease in physical activity contributes to excess energy, leading to fat accumulation (Swinburn et al. 2011). Obesity is associated with a range of serious health problems. Cardiovascular diseases, type 2 diabetes, hypertension, and certain cancer types are strongly linked to obesity. For instance, obesity can lead to insulin resistance, resulting in diabetes (Zimmet et al. 2021). Additionally, obesity increases the risk of hypertension and atherosclerosis, leading to serious complications such as heart attacks and strokes (Lavie et al. 2009). Obesity is also related to musculoskeletal issues like osteoarthritis and psychological disorders such as sleep apnea (Haslam and James 2005).

Gundelia tournefortii is rich in various bioactive components such as phenolic compounds, flavonoids, and essential oils. The high antioxidant capacity of phenolic compounds is known to reduce cellular oxidative stress

(Öztürk and Özçelik 2011). Reducing oxidative stress significantly alleviates insulin resistance, inflammation, and cardiovascular complications associated with obesity (Furukawa et al. 2004).

Gundelia tournefortii also stands out for its anti-inflammatory properties. Obesity is characterized by low-level chronic inflammation, which plays a critical role in the development of insulin resistance, type 2 diabetes, and cardiovascular diseases (Gregor and Hotamisligil 2011). The anti-inflammatory effects of *Gundelia tournefortii* may help prevent such metabolic complications.

Considering the results obtained, significant fat degeneration and coagulation necrosis around the central veins, and congestion in the central veins were observed in the HC group. In contrast, only the HCG1 treatment group showed partially evident fat degeneration around the central veins, but neither necrosis nor congestion was observed. In the other treatment group, hepatocellular degeneration was rare and did not concentrate in any particular area, staying at minimal levels, with no signs of necrosis or congestion observed. It is thought that this hepatoprotective effect may be due to the antioxidant effects of the plants and their beneficial effects on the circulatory system. The likely reason for fat degeneration occurring particularly around the central veins in the liver of the HC group is due to hepatocytes in these areas being most susceptible to hypoxia, and a high-calorie diet possibly exacerbating circulation issues more significantly around the central veins. The reduction in lipolytic activity of hepatocytes due to hypoxia is also considered. Indeed, the congestion in the central veins, which could be interpreted as a circulatory disturbance, was observed only in the HC group, supporting this interpretation.

Similar to our findings, a study by Keleş (2019) on rats fed a high-fat diet also showed sharp-bordered fat vacuoles of various sizes in the centrilobular hepatocytes. Additionally, while coagulation necrosis was observed in some of these hepatocytes, it was prevented in the group fed with Silymarin along with a high-fat diet (Obesity + Silymarin), despite the high-fat diet. In another study, Işık (2019) observed nearly similar morphological changes in the livers of rats on a high-fat diet, noting sharp-bordered fat vacuoles in particularly the centrilobular hepatocytes. However, despite a high-fat diet, *Nigella sativa* fed to one group prevented liver steatosis and degenerative necrotic changes. Furthermore, our study found that the *Gundelia tournefortii* plant extract had a positive effect on the liver tissue of rats fed a high-calorie diet, and these results paralleled the histopathological findings of previous studies (Ejaz et al. 2009; Uyar and Esim 2018). From these studies, Ejaz et al. (2009) showed that curcumin administration and a fatty diet reduced hepatic steatosis in mice. Another study indicated that Mate tea, given in a high-fat diet, could prevent liver damage (Uyar and Esim 2018). Additionally, many studies on plants have reported that foods rich in phytochemicals have hepatoprotective effects against various toxic agents (Bati et al. 2015; Turan and Çelik 2016; Yaman et al. 2016). Polat (2019) noted in their study that treatment with Shepherd's purse in rats with ethanol-induced toxicity reduced some histopathological findings in the liver and improved some liver serum enzyme activities. Moreover, due to their various biological effects, plant-derived compounds have attracted significant attention for their anti-obesity, anti-cancer, and anti-diabetic properties (Engin et al. 2018; Sharifi-Rad et al. 2018; Salehi et al. 2019; Islam et al. 2020). In our study, the experimental groups given the plant extract showed more favorable results in terms of fat degeneration observed in hepatocyte tissues compared to the HC group. Therefore, it was determined that the administration of the plant extract reduced liver steatosis, and these results support the literature. In conclusion, it has been determined that the hepatoprotective effect of the *Gundelia tournefortii* L. plant extract in rats formed with a high-calorie diet may be due to the antioxidant properties of its bioactive constituents.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Idea / Concept: ÖFK, BB
Supervision / Consultancy: ÖFK, BB
Data Collection and / or Processing: ÖFK, BB
Analysis and / or Interpretation: ÖFK, BB
Writing the Article: ÖFK, BB
Critical Review: ÖFK, BB

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