

# Protective effect of *Gundelia tournefortii* extract on spleen tissue in experimental type I diabetes in rats

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## Abstract

**Aim:** In this study, it was aimed to investigate the effects of *Gundelia tournefortii* plant extract on the spleen of rats with experimental type of rats.

**Methods:** In the study, 35 adult Wistar Albino rats were used. Thirty-five male rats were randomly divided into five equal groups of seven rats each. Animal groups were determined as Control, Diabetes, Diabetes + Treatment 1, Diabetes + Treatment 2, Diabetes + Treatment 3. The control group was not exposed to any treatment. The other groups received 45 mg/kg Streptozotocin intraperitoneally on the experimental day. Animals in Diabetes + Treatment 1, Diabetes + Treatment 2 and Diabetes + Treatment 3 groups were administered 50 mg/kg, 100 mg/kg and 200 mg/kg of *Gundelia tournefortii* extract daily by oral gavage for 21 days, respectively. At the end of the experiment, the animals were euthanized, and the spleen was properly removed. The tissues were stained with hematoxylin and eosin after routine tissue tracing.

**Results:** Diabetes mellitus caused a decrease in the diameter of the white pulp and severe atrophy in the spleen tissue. In the red pulp, on the contrary, there was an increase in activation. In the treatment groups, it was determined that *Gundelia tournefortii* extract minimized the damage of diabetes and even the group with images close to the control group was Diabetes + Treatment 3, while in the other treatment groups, the rate of damage repair decreased as the dose decreased.

**Conclusion:** In the study, it was determined that diabetes caused damage to the spleen tissue and these damages were reduced by *Gundelia tournefortii* plant extract. In addition, in the comparison between different doses of this plant extract in the treatment groups, it was determined that the best result was obtained in the group administered at the highest dose of 200 mg/kg.

**Keywords:** Experimental type I diabetes, *Gundelia tournefortii*, protective effect, histopathology

## Introduction

*Gundelia tournefortii*, a member of the Asteraceae family, is a wild edible plant that grows in the temperate regions of Cyprus, Egypt, Iran, Israel, Jordan, Azerbaijan, Turkmenistan, and Turkey [1]. In Turkey, this plant is generally found in high and steep rocky areas of Eastern Anatolia (Erzurum, Erzincan, Tunceli, Elazığ, Malatya), Central Anatolia, and the Mediterranean region [2, 3]. *Gundelia tournefortii*, commonly known locally as kenger grass/gum, has been used in traditional medicine for liver protection, analgesic, antibacterial, antiparasitic, and blood purification reasons [1, 2, 4]. This plant is also reported to be effective in metabolic diseases such as diabetes and hypoglycemia [5]. Phenolic compounds in the chemical composition of the plant are known to play an important role in the prevention of different pathological conditions [6].

The spleen is the second largest lymphoid tissue in the body and plays a major role in hematopoiesis, clearance of red blood cells, and the immune system. It recycles iron, destroys hemoglobin in aged red blood cells as part of the mononuclear phagocyte system, and recycles iron from these cells [7]. Its role in the defense system is to produce antibodies in its white pulp and to remove pathogens from the body through lymph and blood circulation [8]. Monocytes in the red pulp turn into dendritic cells and macrophages, go to damaged areas in the body and affect the repair of the region [9]. In addition to being a lymphoid organ, the fact that the spleen harbors stem cells, which are the precursors of B cells produced in the pancreas, reveals its role in the mechanism of diabetes. Immune deficiency is an important cause of diabetes complications [10]. For these reasons, it has been reported that those whose spleen is removed (splenectomy) are more predisposed to diabetes [11, 12].

Although Type I diabetes is one of the most common chronic metabolic diseases in adults, the incidence of this disease is increasing day by day for many reasons [13]. Therefore, intensive studies on medical and herbal treatment methods to reduce and eliminate the complications of Type I diabetes continue [14]. *Gundelia tournefortii* has been reported to trigger the translocation of Glucose transporter type 4 (GLUT4) protein to the plasma membrane in muscle cells, and there are inferences that alcoholic and hexane extracts of the plant can be used as anti-diabetic [15]. In the literature reviews, there are studies investigating the protective effects of experimental type I diabetes on the spleen and other tissues [16-21]. This study aimed to histopathologically investigate the effects of *Gundelia tournefortii* plant extract on the spleen in rats with experimental type.

## Materials and Methods

### Animal Model

In the study, 35 adult female Wistar Albino rats weighing  $240 \pm 20$  g were supplied from the Experimental Medicine Research and Application Centre of Harran University. All rats were kept in a well-ventilated room under standardized housing conditions, including constant temperature ( $25 \pm 2^\circ\text{C}$ ), a humidity of  $50\% \pm 10\%$ , and a 12-hour light/12-hour dark cycle. All experimental animals were fed with a standard laboratory-balanced commercial diet and drinking water ad libitum. The animal handling and the study protocol were ethically approved by the Animal Experiments Local Ethics Committee of Harran University (2023-008-09).

### Animal groups and treatment schedule

Thirty-five male rats were randomly assigned into five equal groups of seven rats each. Animal groups were determined as Control, Diabetes, Diabetes + Treatment 1, Diabetes + Treatment 2, Diabetes + Treatment 3. The control group was not exposed to any treatment. The other groups (Diabetes, Diabetes + Treatment 1, Diabetes + Treatment 2, Diabetes + Treatment 3) were administered 45 mg/kg Streptozotocin (to be dissolved in cold citrate buffer) intraperitoneally on the experimental day. Ad libitum access to water containing 10% sugar was provided for 48 hours to prevent hyperglycemia. Animals in the diabetes group were given 0.25 ml of sterile water by oral gavage daily for 21 days. Animals in Diabetes + Treatment 1, Diabetes + Treatment 2, and Diabetes + Treatment 3 groups were administered 50 mg/kg, 100 mg/kg, and 200 mg/kg of *Gundelia tournefortii* extract daily by oral gavage for 21 days, respectively. At the end of the experiment, animals were sacrificed under general anesthesia (Xylazine 10 mg/kg and Ketamine 5 mg/kg), and spleen tissues were removed under appropriate storage conditions [19].

### Histopathological examination

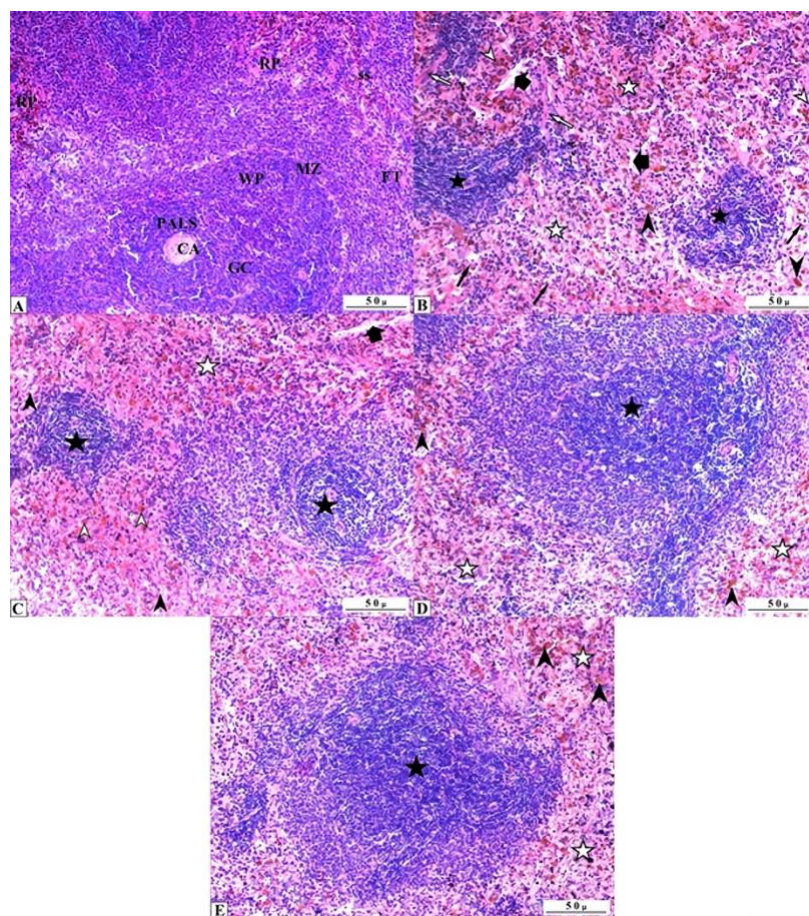
The tissue samples were fixed in 10% neutral buffer solution. After the fixation process was completed, the specimens were washed in tap water, formol was removed, and routine tissue tracing procedures were performed by passing through alcohol-xylol and paraffin slides. The tissue traced samples were paraffin-blocked. Each paraffin block was sectioned on 4μ thick normal slides with the help of a rotary microtome (Leica RM-2135, Leica Microsystems Inc., Bensheim, Germany). After 1 hour in the oven, the tissues were passed through

the xylol-alcohol series for deparaffinization and rehydration and kept in distilled water. The hematoxylin-stained tissues were then decolorized in running tap water and stained with eosin. Finally, the tissues were dehydrated in alcohol, cleaned in xylol, and then covered with a coverslip by dropping Entellan® (Merck, Darmstadt, Germany, Nr:107961). Hematoxylin and eosin-stained slides were examined under the light microscope (Olympus BX51™, Olympus Corporation, Tokyo, Japan), and histopathologic findings were scored as absent (-), mild (+), moderate (+++), and severe (++++ according to severity [22, 23].

## Results

Histopathologic examination of the study tissues revealed that the spleens of healthy rats in the control group had normal histologic appearance and did not carry any pathologic lesions. In this group, billroth cords in which normal splenocytes were located, red pulps consisting of venous sinusoids, and white pulps consisting of large nodules of lymphoid accumulation adjacent to or within the periarterial lymphoid sheaths surrounding the central artery were observed (Figure 1A). In the spleen

tissues of the rats in the diabetes group, the diameter of the white pulp was significantly decreased, and an increase in the activation of the red pulp was detected in contrast to the severe atrophy of this tissue. It was observed that fibrous trabeculae thickening the reticular roof of the spleen became prominent due to degeneration in the marginal zone between the white pulp and red pulp. Numerous hemosiderin-laden macrophages were found in the enlarged red pulp due to severe sinusoidal congestion and hemolysis. In addition, vacuolization of degenerated splenocytes was observed in the red pulp parenchyma (Figure 1B). In the Diabetes+50 mg group, activation in the red pulp was slightly decreased, and the diameter of the atrophied white pulp was slightly enlarged compared to the diabetes group. Similarly, destruction in the spleen was less in the diabetes group (Figure 1C). In the Diabetes+100 mg group, white pulp development was better than in the Diabetes+50 mg group, and vacuolization in parenchymal cells and congestion in sinusoids decreased (Figure 1D). In the Diabetes+200 mg group, white pulp development was better than in the Diabetes+100 mg group, and a histologic appearance almost similar to the control group was observed, and vascular and degenerative changes in the splenic tissue were observed to be considerably less (Figure 1E).



**Figure 1.** (A) Normal histological appearance red pulp (RP), white pulp (WP), peri arterial lymphatic sheath (PALS), central arteriole (CA), germinal center (GC), fibrous trabecula (FT), marginal zone (MZ), splenic sinus (ss) in control group; (B) Severe atrophy of white pulp (asterisks), increased red pulp activation (hollow asterisks), hemosiderin-laden macrophages (arrowheads), sinusoidal congestion (hollow arrowheads), splenocyte vacuolization (thin arrows), fibrous trabeculae prominence after parenchymatous degeneration (thin hollow arrows), sinusoidal dilatation (thick arrows) in the diabetes group; (C) Atrophy of white pulp (black stars), increased activation of red pulp (hollow star), hemosiderin-laden macrophages (arrowheads), vacuolization of parenchymal cells (hollow arrowheads), sinusoidal dilatation (thick arrow); (D) Increase in white pulp diameter (black asterisk), activation of red pulp (hollow asterisk), hemosiderin-laden macrophages (arrowheads); E. Near-normal enlargement of white pulp diameter (black asterisk), near-normal activation in red pulp (hollow asterisk), hemosiderin-laden macrophages (arrowheads), Rat, Spleen, H&E, 50µ, x200.

In the histopathologic examination, it was noted that the diameter of the white pulp was considerably smaller in the diabetic groups; the diameter of the white pulp increased in parallel with the dose increase in the

treatment groups, and the pathologic lesions in the red pulp in the diabetes group decreased with the dose increase in the treatment groups (Table 1).

**Table 1.** Histopathological finding scoring in experimental groups.

| Experimental groups  | WPA | RPA | PCV | HLM | SSC | FTT |
|----------------------|-----|-----|-----|-----|-----|-----|
| Control              | -   | -   | -   | -   | -   | -   |
| Diabetes             | +++ | +++ | +++ | +++ | +++ | ++  |
| Diabetes+Treatment 1 | ++  | ++  | ++  | +++ | ++  | +   |
| Diabetes+Treatment 2 | +   | ++  | ++  | ++  | +   | +   |
| Diabetes+Treatment 3 | +   | +   | +   | +   | +   | -   |

WPA; White pulp atrophy, RPA; Red pulp degenerative activation, PCV; Parenchymatous cell vacuolization, HLM; Hemosiderin laden macrophages, SSC; Splenic sinusoidal congestion, FTT; Fibrous trabecular thickening. Histopathological scoring: none (-), mild (+), moderate (++), severe (+++).

## Discussion

Diabetes mellitus, which is an important health problem for humans, has been studied many times, and it is still one of the most frequently studied subjects in the scientific world [19, 20, 24]. In many of these studies, histopathologic examination was performed, and it was revealed that diabetes has a splenotoxic effect. In some studies, some substances have been reported to reduce spleen tissue damage due to experimental diabetes [16-18].

Prangthip et al. [17] investigated the effect of Riceberry on diabetes in rats. In their study, they reported that in diabetic rats, the white pulp shrunk, the red pulp expanded and underwent degenerative changes, and they also found a large number of hemosiderin-laden macrophages and vacuolized splenocytes in the red pulp, but these findings decreased with the addition of Riceberry to the rations.

Ghosh et al. [18] investigated the effect of ferulic acid against diabetes-induced spleen damage and reported that ferulic acid significantly reduced the reduction in the diameter of the white pulp and the accumulation of hemosiderin granules in the red pulp in the diabetic spleen.

El-Desouki et al. [16] suggested that vitamin D and coconut oil reduced white pulp atrophy and severe destruction of red pulp in diabetic mice, suggesting that vitamin D is particularly effective in this case.

Malini et al. [21] noted that PLGA nanoparticles synthesized from Jengkol bark extract reversed pathological lesions in diabetic rat spleens.

Mohamed et al. [25] investigated the effect of L-carnitine on diabetic spleen tissue damage. In their study, they reported that destructive pathological lesions were formed in the spleens of diabetic animals, and improvement was observed in these lesions in the treatment groups.

Hacioglu et al. [26] examined the therapeutic effects of *Cistus laurifolius* extract and metformin in the treatment of streptozotocin-induced diabetes and suggested that these active substances, especially *Cistus laurifolius* extract, contributed to the healing of diabetic spleen damage.

Ebaid et al. [27] investigated the protective effect of whey proteins obtained from camel milk on diabetic spleen injury and found that camel whey proteins slowed down the reduction in the diameter of white pulp due to diabetes.

Hanchang et al. [28] investigated the effect of hesperidin on diabetic spleen damage and reported that hesperidin developed a protective effect against diabetes-induced spleen damage. In most of the previous studies, diabetes was reported to cause spleen tissue damage, but García-Galicia et al. [29] and Draganescu et al. [30] reported normal histological appearance in the spleens of diabetic animals. In our study, it was observed that diabetes caused pathologic changes in spleen histomorphology in accordance with most previous studies. In previous studies, the protective effects of some substances against diabetes-induced toxicity were investigated [16, 18, 21, 23, 28].

In addition, some previous studies have investigated the protective effects of *Gundelia tournefortii* extract in different experimental models and reported positive effects [31, 32]. However, no study was found in which the effect of *Gundelia tournefortii* extract was observed against spleen tissue damage induced by diabetes. In our study, shrinkage of the white pulp, severe destruction of the red pulp, and associated hemosiderosis, vacuolization, and sinusoidal congestion in the parenchyma were observed in diabetic animals. In parallel with the use of increasing amounts of *Gundelia tournefortii* extract, it was determined that the pathological lesions observed decreased.

## Conclusion

Diabetes has been a major health problem for many years, and today, it attracts the attention of the scientific world. Therefore, many studies have been conducted on diabetes, and the presence of protective substances against the damage of diabetes in various tissues has been investigated.

In our study, it was determined that diabetes has a severely destructive effect on the spleen, an important immune organ, and that this destruction can be prevented by the application of *Gundelia tournefortii* extract. Although it cannot be said that *Gundelia tournefortii* eliminates diabetes, it was observed that it contributed to the reduction of lesions formed in the spleen tissue due to diabetes, and it was emphasized that more comprehensive studies are required to be an alternative substance.

## Disclosures

**Ethics Committee Approval:** Ethics committee approval was received for this study from Animal Experiments Local Ethics Committee of Harran University, with the approval number: 2023-008-09.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - M.D.; Design - M.D., M.B.D.; Supervision - M.D., M.B.D.; Materials - M.D., M.B.D.; Data collection &/or processing - M.B.D.; Analysis and/or interpretation - M.B.D.; Literature search - M.D., M.B.D.; Writing - M.D., M.B.D.; Critical review - M.B.D.

**Conflict of Interest:** There is no any conflict of interest.

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