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Original Article HISTOLOGY & EMBRYOLOGY

# Hydroxytyrosol has a protective effect on the kidneys through dardarin and spexin

**Nevin Kocaman,[1] Elif Onat,[2] Serhat Hancer[1]**

[1]Department of Histology and Embryology, Firat University Faculty of Medicine, Elazig, Turkiye
[2]Department of Medical Pharmacology, Adiyaman University Faculty of Medicine, Adiyaman, Turkiye

## ABSTRACT

**OBJECTIVE:** In this study, the possible role of dardarin and spexin in the protective effect of hydroxytyrosol (HT) against corn syrup-induced renal injury in rats was investigated.

**METHODS:** Rats were categorized into four groups (n=6) as control, HT, corn syrup, and corn syrup+HT. Over 6 weeks, rats were administered water infused with 30% corn syrup, 4 ml/kg/day solution containing HT was administered, both independently and in conjunction with corn syrup, throughout the 6 weeks. The molecular parameters of dardarin and spexin in the renal tissue were assessed through histopathological examination. Biochemical parameters were also examined with the ELISA Method.

**RESULTS:** In this study, it was observed that the dardarin and spexin levels increased in the control group as a result of the administration of corn syrup. After HT treatment, it was observed that the dardarin and spexin levels decreased. The increase in glucose, amylase, and lipase levels because of corn syrup consumption decreased with hydroxytyrosol consumption. The increase in erythrocyte extravasation, exudate accumulation, and fibrosis in kidney tissue observed as a result of corn syrup decreased as a result of HT administration.

**CONCLUSION:** It is thought that the protective effect of HT against damage to the renal due to corn syrup consumption may be mediated by dardarin and spexin.

*Keywords: Corn Syrup; dardarin; hydroxytyrosol; kidney; spexin.*

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It has been determined that the likelihood of chronic kidney disease increases by 60% in people who consume high-calorie and high-fructose drinks [1]. The underlying cause of kidney disease due to high fructose intake; It is thought that there may be an increase in serum uric acid, an increase in vasopressin level, and postprandial hypertension due to fructose intake [2, 3]. It has been observed that ingestion of foods containing high fructose corn syrup (HFCS) increases renal vascular resistance and increases renal vasoconstriction due to sympathetic system activation [4]. Consumption of beverages containing HFCS may aggravate renal vasoconstriction tone and therefore increase the risk of nephropathy due to renal ischemia. For these reasons, long-term consumption of large amounts of fructose is thought to be associated with kidney diseases [3].

Extra virgin olive oil (EVOO) is the most important antioxidant component in the Mediterranean diet [5, 6]. The protective effect of EVOO on the kidneys due to its antioxidant properties has been confirmed in experimental nephropathy models [7, 8]. The most important of

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Correspondence: Elif ONAT, MD. Adiyaman Universitesi Tip Fakultesi, Tibbi Farmakoloji Anabilim Dali, Adiyaman, Turkiye.
Tel: +90 505 938 64 45 e-mail: eonat@adiyaman.edu.tr

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the polyphenolic compounds in EVOO is hydroxytyrosol (HT), which has a strong antioxidant effect [9]. It has been shown that the administration of extra virgin olive oil rich in polyphenols to patients with chronic kidney disease improves the renal analytical profile more than in patients given extra virgin olive oil poor in polyphenols. This nephroprotective effect is thought to be related to the antioxidant property of HT [10].

Dardarin (LRRK2), which has a protein structure, is found in the brain, lungs, and to a lesser extent, in some other tissues. Known as a protein with multiple domains, LRRK2 has GTPase and protein kinase activities. They also have important roles in many cellular events and signaling pathways, including the cytoskeleton, vesicle transport, mitochondrial metabolism, and the regulation of endocytosis and autophagy [11]. LRRK2 is known to have many functions in the body, but its full functional role is not elucidated yet.

Spexin is a peptide hormone that is a member of the spexin/galanin/kisspeptin group [12, 13]. Spexin is found in many tissues such as ovaries, testicles, heart, skeletal muscle, kidney, lung, liver, pancreas, brain, thyroid, adrenal gland, spleen, adipose tissue, stomach, and gastrointestinal tract [14]. Spexin stimulates galanin receptor types 2 (GALR2) and 3 (GALR3) in target cells [15]. It also plays a role in many functions in the body, such as feeding, energy regulation, lipid accumulation, blood pressure, water/salt balance, cardiovascular, and renal functions, and cardiorenal responses [16–18]. Various studies have shown that this hormone can regulate inflammatory processes, but the underlying mechanism is not yet clear [19].

In this study, it was investigated whether LRRK2 and spexin molecules play a role in the protective effect of HT against kidney damage caused by corn syrup consumption in rats.

**Highlight key points**

- Corn syrup consumption may cause damage to the kidneys.
- HT may have a protective effect on kidney damage caused by corn syrup consumption.
- Dardarin may be an important molecule in the diagnosis of kidney damage.
- Spexin is a new peptide and may be a precursor of kidney damage.
- Dardarin and spexin may be important target molecules in the treatment of kidney diseases.

## MATERIALS AND METHODS

### Animals and Experimental Design

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies [20]. The Animal Ethics Committee of Adıyaman Unıversity approved the study protocol (Protocol no: 2024/031). The experiments were performed according to the "Guide for the Care and Use of Laboratory Animals". The study was conducted in accordance with the Declaration of Helsinki. In the study, 24 male Sprague-Dawley rats, weighing 200-250 g, aged 8-10 weeks, obtained from the Adıyaman University Animal Experimental Research Center were used. The rats were housed in a fixed environment. They were provided with standard food and water consumption during the study. The rats were divided into four groups, 6 animals in each group: Group I: control, Group II: HT, Group III: corn syrup, Group IV: corn syrup + HT. No application was made to the control group during the experiment. Hydroxytyrosol (HT) was supplied by Kale Naturel Herbal Products Company in Turkey. HT was given orally to rats in Groups II and IV at a dose of 4 ml/kg/day for 6 weeks. 30% corn syrup was added to the drinking water of rats in Groups III and IV for 6 weeks [21]. At the end of this period, rats were administered intraperitoneal ketamine (75 mg/kg) + xylazine (10 mg/kg) and blood was taken from their hearts. Kidney tissues were placed in 10% formaldehyde solution for immunohistochemical examinations.

### Serological Analysis

Cardiac blood samples of the nonfasted rats were centrifuged at 4° and 10.000 g for 30 min. Serum samples were immediately stored at -80° until the samples were assayed. Analysis for glucose, amylase, lipase, insulin and uric acid levels was performed spectrophotometrically on an Architect c16000 biochemistry autoanalyzer (Abbott Diagnostics, USA) with commercially available kits from Abbott Diagnostics.

### Histochemical Examination

Histological follow-up series were applied to the kidney tissues taken and then embedded in paraffin blocks. Sections were taken from these blocks (5 μm). They were stained with Hematoxylin & Eosin, Masson Trichrome, and Immunohistochemically.

TABLE 1. Levels of various biochemical parameters in blood serum of rats

| Groups | Control | HT | Corn syrup | Corn syrup+HT |
|---|---|---|---|---|
| Glucose (mg/dl) | 178.33±4.08 | 203.67±50.62 | 460.33±63.53[ab] | 194±22.18[c] |
| Amylase (U/L) | 1583.3±40.82 | 1731.5±40.42 | 2572.2±281.38[ab] | 1763.8±139.23[c] |
| Lipase (U/L) | 9.17±0.41 | 11.33±1.03 | 15±2.45[ab] | 11.5±0.84[c] |
| Insulin (uIU/ml) | 0.03±0.02 | 0.028±0.02 | 0.06±0.02 | 0.04±0.01 |
| Uric acid (mg/dl) | 0.75±0.05 | 1.15±0.5 | 3.77±3.45 | 1.35±0.3 |

Error bars indicate SD; HT: Hydroxytyrosol; a: P<0.05 compared to the control group; b: P<0.05 compared to HT group; c: P<0.05 compared to corn syrup group.

### Immunohistochemical Examination

Kidney tissues from rats were embedded in paraffin blocks after undergoing a histological follow-up series and 5 μm thick sections were taken from these blocks for immunohistochemical staining [22]. Histological tissue microarray slides of 3 μm thickness were used for immunohistochemical staining (IHC). LRRK2 primary antibody (orb500678; Biorbyt Ltd., Cambridge, England) and spexin primary antibody (A04088-1, booster biology technology, Pleasanton, CA, USA) were used as antibodies. The evaluation was performed on a Zeiss Axio Scope A1 microscope (Carl Zeiss Microscopy GmbH 07745 Jena, Germany). After immunohistochemical staining, histoscoring was performed for LRRK2 and spexin. As a result of microscopic evaluation of staining intensity: Negative colored areas were given a value of 0, areas showing less than 25% staining were given a value of 0.1, areas showing 26–50% staining were given a value of 0.4, areas showing 51–75% staining were given a value of 0.6, and areas showing staining close to homogeneity (76–100%) were given a value of 0.9. The formula used in the histoscore was as follows.

Histoscore = Distribution x Intensity [22].

### Statistical Analysis

#### Power Analysis

In this study, G power 3.1.9.7v program ANOVA fixed effects procedure was used to calculate the sample sizes of the groups. Considering Effect size: 0.90, statistical power (1 - β): 0.90 and significance level 0.05 as bidirectional, actual power was determined as 0.90, and 6 animals for each group (4 groups) for a total of 24 animals.

Statistical analyses were performed using SPSS 22 (SPSS Statistics 21.0 (Armonk, New York: IBM Corp.). The conformity of quantitative data to normal distribution was evaluated with the Shapiro-Wilk test. The One-Way ANOVA Test and the Tukey HSD Test were used for post-hoc multiple comparisons. Study results are presented as mean±SD, indicating the level of statistical significance ($p<0.05$).

## RESULTS

### Biochemical Findings

Plasma glucose, amylase, and lipase levels in rats given corn syrup were significantly increased compared to both groups (control, HT) ($p<0.001$). Plasma glucose, amylase, and lipase values were lower in the corn syrup group as a result of HT administration ($p<0.001$). Plasma insulin and uric acid values were higher in rats given corn syrup than in both groups (control and HT) but were not significant. Plasma insulin and uric acid values were lower in rats given corn syrup as a result of HT administration, although not significant (Table 1).

### Histochemical Findings

As a result of the staining of the groups with Hematoxylin-Eosin and Masson trichrome, the control and HT groups were seen as normal (Table 2, Fig. 1, 2). In the Corn Syrup group, there was an increase in erythrocyte extravasation, exudate accumulation, and fibrosis compared to the control and HT groups ($p<0.001$). Compared to the Corn Syrup Group, a significant decrease in erythrocyte extravasation, exudate accumulation, and fibrosis was observed in the Corn Syrup+HT Group ($p<0.001$) (Table 2, Fig. 1, 2).

### Immunohistochemical Findings

In the kidney tissue with immunohistochemical staining, LRRK2 immunoreactivity increased sig-

**Table 2.** Histopathologic findings of the renal tissues (hematoxylin and eosin-Masson trichrome)

| Parameters | Control | HT | Corn syrup | Corn syrup+HT |
|---|---|---|---|---|
| Erythrocyte extravasation | 1.43±0.53 | 1.71±0.49 | 5.57±0.79$^{ab}$ | 2.29±0.49$^{c}$ |
| Exudate accumulation | 1.43±0.53 | 1.29±0.49 | 6.71±0.49$^{ab}$ | 1.71±0.49$^{c}$ |
| Fibrosis | 1.43±0.53 | 1.29±0.49 | 4.71±0.49$^{ab}$ | 2.86±0.69$^{abc}$ |

Error bars show SD; HT: Hydroxytyrosol; a: P<0.05 compared to control; b: P<0.05 compared to HT; c: P<0.05 compared to corn syrup.

**Table 3.** Immunohistochemical results for dardarin in the renal tissues

| Groups | Control | HT | Corn syrup | Corn syrup+HT |
|---|---|---|---|---|
| Dardarin | 0.21±0.07 | 0.2±0.06 | 0.4±0.07$^{ab}$ | 0.27±0.05$^{c}$ |

Error bars indicate SD; HT: Hydroxytyrosol; a: P<0.05 compared to the control group; b: P<0.05 compared to HT group; c: P<0.05 compared to corn syrup group.

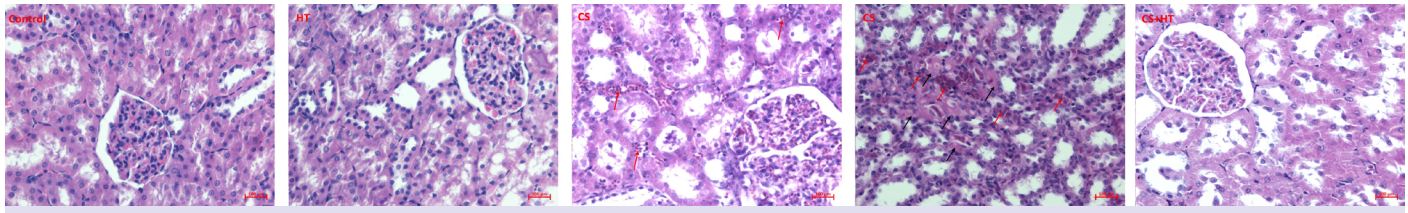


**Figure 1.** The histopathological findings of renal tissues of observation (hematoxylin and eosin).

HT: Hydroxytyrosol; CS: Corn syrup; CS+HT: Corn syrup+ Hydroxytyrosol.

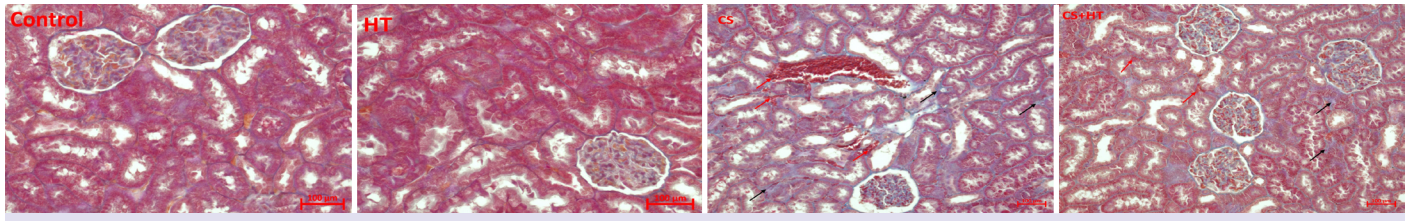


**Figure 2.** The histological findings of renal tissues of observation (Masson trichrome staining).

nificantly as a result of corn syrup application compared to the two groups (control, HT) (p<0.001). In contrast, LRRK2 immunoreactivity was lower in the corn syrup group as a result of HT application (p=0.005) (Table 3, Fig. 3).

Specin immunoreactivity increased as a result of corn syrup application compared to two groups (control, HT) (p<0.001). Specin immunoreactivity was lower in the corn syrup group as a result of HT application (p<0.001) (Table 4, Fig. 4).

## DISCUSSION

In the study, the effect of HT, which is thought to have a protective effect on rats whose kidneys were damaged by consuming corn syrup, and whether new proteins such as LRRK2 and spexin were involved in this effect was examined. As a result of this examination, it is thought that HT has a protective effect against the negative changes caused by corn syrup in the kidneys and that LRRK2 and spexin may also play a role in this effect.

TABLE 4. Immunohistochemical results for SPX in the renal tissues

| Groups | Control | HT | Corn syrup | Corn syrup+HT |
|---|---|---|---|---|
| SPX | 0.36±0.08 | 0.34±0.07 | 0.94±0.21[ab] | 0.51±0.08[c] |

Error bars indicate SD; HT: Hydroxytyrosol; SPX: Spexin; a: P<0.05 compared to the control group; b: P<0.05 compared to HT group; c: P<0.05 compared to Corn Syrup group.

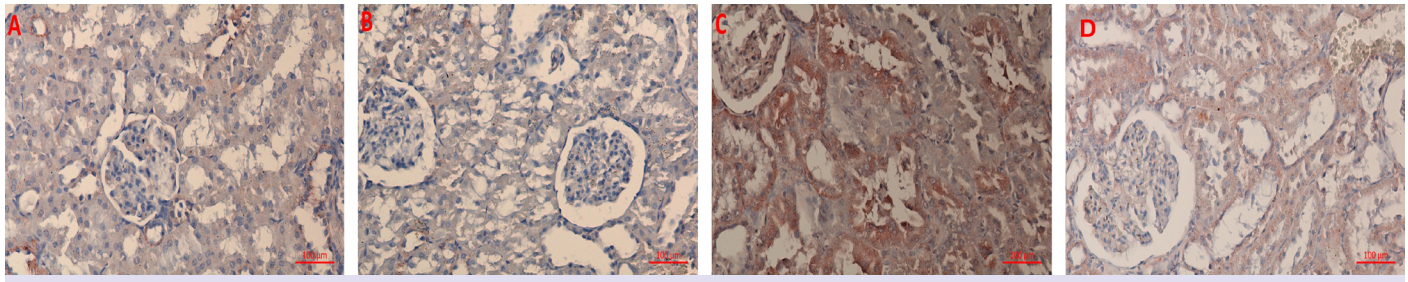


FIGURE 3. Immunohistochemical findings for dardarin in renal tissues (control, HT, corn syrup, corn syrup+HT).

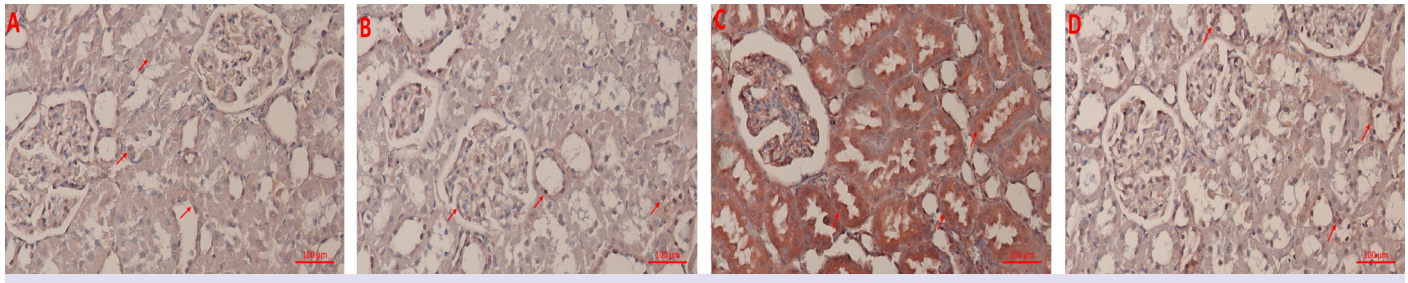


FIGURE 4. Immunohistochemical findings for spexin in renal tissues (control, HT, corn syrup, corn syrup+HT).

It has been suggested that the Mediterranean diet, which has important antioxidant properties, has a protective effect on diabetic nephropathy [23]. When the structure, hydrophilic properties, metabolism, and transformations of the HT molecule, the most important antioxidant component in EVOO, were examined, it was observed that its conjugated metabolites were mainly excreted by the kidneys [24]. HT accumulates in the kidneys until it is excreted from the body [25] and in the meantime, it may have a nephroprotective effect thanks to its antioxidant properties [26]. These antioxidant properties explain the protective effect of HT on the kidneys from a morphological and functional perspective. A previous study showed that it has been shown that the administration of extra virgin olive oil rich in polyphenols to patients with chronic kidney disease improves the renal analytical profile more than in patients given extra virgin olive oil poor in polyphenols [5]. In our study, consistent with these findings, plasma glucose, amylase, lipase, insulin, and uric acid levels increased with corn syrup and decreased as a result of HT application, proving once again the protective effect of HT on blood glucose-insulin regulation and the kidney. In addition, it was observed that the increase in erythrocyte extravasation, exudate accumulation, and fibrosis observed in the renal tissue as a result of corn syrup application was significantly reduced as a result of HT application.

Numerous studies have revealed that LRRK2 is functionally involved in a wide variety of cellular events, including inflammation, autophagy, apoptosis, synaptogenesis, and proliferation [27, 28]. It has been shown that LRRK1 and LRRK2 play important roles in regulating protein homeostasis and that the LRRK2 −/− kidney undergoes a large loss of LRRK compared to other organs, thus aging. LRRK2-dependent molecular and cellular changes are likely to be

responsible for increased cell death and inflammatory responses [29]. Drugs that inhibit LRRK2 to treat PD have been shown to induce pathologies in peripheral organs, especially the kidneys and lungs [30]. Since LRRK2 is found at high levels in papillary renal cell carcinoma (pRCC), inhibition of LRRK2 kinase is important for its effect on the kidney [31, 32]. Disruption of LRRK2 expression in pRCC cells leads to cell cycle arrest and inhibition of crucial cell signaling pathways due to impaired growth factor receptor-dependent stimulation. Moreover, genetic deletion of LRRK2 in mice caused significant pathologies in the lung and kidney, suggesting that long-term inhibition of LRRK2 enzymatic activity in Parkinson's disease may be particularly detrimental to these organs and therefore this treatment approach is not appropriate. LRRK2 amplification and overactivity are implicated in the subgroup of type I papillary renal cell carcinoma, which accounts for approximately 10% of kidney cancer [33]. In our study, the increase in the LRRK2 molecule in the kidney due to corn syrup intake suggests that LRKK2 may play a role in inflammation and apoptotic pathways in the kidney. The decrease in the amount of LRRK2 in rats receiving HT at the same time as corn syrup suggests that LRRK2 may play a role in the healing properties of HT against the kidneys. However, more studies are needed on the effect of LRRK2 in this pathology to say this.

It has been shown that SPX can reduce oxidative stress and inflammation in those who develop kidney failure due to excess weight [14]. It has been shown that SPX treatment stimulates an inflammatory response by regulating cytokine and chemokine levels in chronic renal failure [34]. In another study, it was observed that as a result of SPX application, oxidative stress in the kidneys decreased, and inflammation in renal dysfunction caused by obesity decreased [14]. Additionally, a protective effect on kidney damage was observed as a result of intracerebroventricular administration of SPX [35]. However, in chronic renal failure due to adenine, SPX application showed an inhibitory effect on renal damage and inflammation [36]. In another study, it was observed that spexin-based (galanin receptor) GALR2 agonists improved diabetic nephropathy without changing metabolic syndrome parameters [37]. A recent study observed pathological changes in kidney tissue, increased oxidative stress and apoptosis, and elevated SPX levels as a result of exposure of rats to aluminum. Additionally, it has been observed that pathological changes and elevated SPX levels caused by aluminum are reduced by NAC administration, and nephrotoxicity is prevented prophylactically [38]. In another study, increased SPX immunoreactivity in kidney tissue was observed in ADR-induced nephrotoxicity. However, a significant decrease in SPX levels was observed in the ADR + NAC group in response to the decrease in oxidative stress and apoptosis [39]. In our study, we think that the increase in SPX levels in rats given corn syrup may help prevent damage to the kidney tissue due to oxidative stress and apoptosis caused by corn syrup. The decrease in SPX levels after HT treatment suggests that HT may have a protective effect on nephrotoxicity by affecting SPX levels, which are thought to maintain the balance between oxidative stress and apoptosis.

This study suggests that LRRK2 and spexin may be effective in the healing properties of HT against the pathological processes induced by corn syrup in the kidneys. However, the mechanisms involved in this effect need to be further investigated. In addition, these results need to be supported by analysis tests such as Western Blot and PCR and their clinical aspects must also be investigated.

## Conclusion

It is thought that HT has a healing effect on corn syrup-induced kidney damage and that newly discovered molecules such as LRRK2 and spexin may play a supporting role in this effect. LRRK2 and spexin may be important markers in screening and monitoring treatment protocols for kidney diseases.

**Ethics Committee Approval:** The Adiyaman University Animal Experiments Ethics Committee granted approval for this study (date: 02.05.2024, number: 2024/031).

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