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Original Article

Effects of Saint John's wort on the fetus in pregnant rats

Gebe sıçanlarda kantaron otunun fetüse etkisi

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ABSTRACT

Introduction: Because of the toxic and teratologic side effects that might develop into the fetus, the number of drugs that can be used in the treatment of depression seen in pregnancy is very limited. In this study, we investigated whether the Saint John's wort used during pregnancy has side effects on the liver of fetus.

Methods: Thirteen Wistar albino female rats were used in this study. The animals divided into two groups as 8 rats for the experimental group and 5 rats for the control group. The animals detected for pregnancy in the experimental group were fed with the Saint John's wort extract as 100 mg/kg/day through orogastric probe from the first day of the pregnancy. The animals in the control group were fed with 2 ml distiled water through an orogastric probe every day begining from the first day of the pregnancy. The newborn pups were taken. Their liver tissues were harvested and investigated after the tissue processing and staining procedure.

Results: Microvesicular lipidosis and hydropic degeneration were observed in histopathological evaluation of the harvested tissues of experimental group.

Conclusion: As a result, there is not enough data in the literature in order to claim that Saint John's worth is reliable for the pregnant women or fetus. It is important for the physician to evaluate the complaints related to the use of pregnancy and to raise the awareness of the physicians in the first stage of the pregnancy follow-up. For the usage of this herb as an alternative or addition to antidepressive drugs more preclinical (basic) and clinical studies need to be performed.

Keywords: Saint John's wort, fetus, liver

ÖZ

Giriş: Fetüste gelişebilecek toksik ve teratolojik yan etkilerinden dolayı, gebelikte görülen depresyonun tedavisinde kullanılabilecek ilaç sayısı oldukça sınırlıdır. Çalışmamızda, gebelik sırasında depresyon tedavisi için halk arasında sık kullanılan kantaron otunun fetüs karaciğeri üzerine yan etkilerini araştırdık.

Yöntem: Çalışmada kullanılan 13 adet dişi Wistar albino sıçan, 8 adet deney grubu, 5 adet de kontrol grubu olmak üzere ayrıldı. Gebe kalmaları sağlanan deney grubundaki hayvanlara, gebeliğin ilk gününden itibaren, gebelik süresince 100 mg/kg/gün kantaron otu ekstresi orogastrik sonda yardımıyla verildi. Kontrol grubundaki sıçanlara ise gebeliğin ilk gününden itibaren her gün 2 ml distile su orogastrik sonda yardımıyla verildi. Doğan yavruların karaciğer dokuları çıkarıldı, %10 nötral formalin ile fiksasyonu yapıldı, alkol takibinden sonra parafin blokları hazırlandı, alınan kesitler hematoksilen ve eosin ile boyanarak incelendi.

Bulgular: Deney grubuna ait karaciğer dokularının histopatolojik değerlendirmesinde mikroveziküler yağlanma ve hidropik dejenerasyon gözlendi.

Sonuç: Kantaron otunun gebe kadınlar veya fetus açısından güvenilir olduğunu iddia etmek için yeterli bilgi bulunmadığı sonucuna varıldı. Bu otun gebelik kullanımıyla ilgili sakıncaların hekimler tarafından değerlendirilmesi ve özellikle birinci basamakta hekimlerin, gebe takiplerinde hastaları bu konuda bilinçlendirmesi önem arz etmektedir. Kantaron otunun gebelikte kullanımı ve gerek anne gerek fetüste tüm vücuttaki etkilerinin ortaya konması için daha ileri çalışmalar yapılması gerekmektedir.

Anahtar Kelimeler: Kantaron otu, fetüs, karaciğer

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Introduction

Saint John's Wort (Hypericum perforatum) is a plant of the Hypericaceae family [1]. In various regions of Turkey, it is known as "Binbirdelik otu", "Kılıç otu", "Mayasıl otu", "Yara otu", and "Kuzu kıran" [2]. Saint John's Wort has been used since ancient times in psychiatric diseases, wound healing, digestive problems, burns, and infections [1]. Especially because of its antidepressant effect, it reaches millions of dollars sales every year in the United States and Europe [3]. It has been reported in Germany that this herb is prescribed more than antidepressant drugs [4].

At least nine groups of substances are shown contributing to the pharmacological effects of Saint John's Wort [5]. From these substances, it has been reported that hypericin and hyperforin are the predominant molecules responsible for the antidepressant effects of the plant [6,7]. These molecules may inhibit the enzyme monoamine oxidase (MAO), and may also lead to an increase in serotonin, dopamine, and norepinephrine levels [8].

Saint John's Wort has been used as a remedy in psychiatric disorders since ancient times. Hippocrates and Galen are also reported to use this herb to rescue people from the evil spirits [9]. Presently, its use as an herbal alternative to synthetic antidepressants has worldwide popularity. In the treatment of mild to moderate depression, this herb was proved to be as effective as synthetic antidepressant medications with perfect tolerability [10].

Depression reduces the quality of life by deteriorating human function, creativity, happiness, and satisfaction, and leads to substantial workforce losses [11]. International studies indicate that vast majority of depression is seen among women between the ages of 18 and 44, including fertility processes such as pregnancy, childbirth, and puerperium [12, 13]. These processes are a part of the natural life of women, which include a high risk of encountering many important biological and psychosocial changes and the risk of facing factors that can cause anxiety and stress [14]. Mild to moderate depression is the most common psychiatric disorder in pregnancy. Depression during pregnancy can create some biological risks for the mother and the baby [13].

Called "the herbal Prozac", the Saint John's Wort is frequently used in the population [15, 16]. Among women, who are more prone to use alternative treatment methods, this herb is usually accepted as harmless due to its natural origin. Therefore, the Saint John's Wort can be consumed uncontrolled in all periods of the pregnancy, exposing the fetus to side effects of this plant [17].

However, if we look at the literature, it is seen that the effects of this herb on the fetus have not yet been clarified. The effects of the plant on fetal growth and development, as well as the possible pathological effects on the liver, where the agent is metabolized, are vastly obscure.

This study aimed to evaluate the histopathological effects of non-prescribed and uncontrolled Saint John's Wort use on the fetal liver tissue in the treatment of depressive symptoms during pregnancy, and also to investigate its effects on the height and weight of the newborn, revealing the effects on growth and development.

Methods

Sheltering of the Animals

Thirteen female Wistar Albino rats obtained from Gaziantep University Medical Faculty Experimental Animals Laboratory and weighing between 170-200 grams were used in the study. Before starting the experiment, the animals were separated from each other for one week, put into wire chambers in rooms where ambient light was set at 12 hours light and 12 hours dark, and the room temperature was fixed at 21 ± 1 °C for acclimatization. During the experiment, all animals were fed with standard feed and tap water.

For the experiment, consent was obtained from the Gaziantep University Animal Experiments Local Ethics Committee with the approval number 06-2008 / 113.

Experimental Model

The rats were randomly assigned into experimental (8 rats) and control (5 rats) groups. The two groups were as follows:

Group 1: Control group (Given distilled water; n=5)

Group 2: Experimental group (Given Saint John's Wort; n=8)

The animals in the experimental group were placed in two cages, with four animals in each. All of the animals in the control group remained in the same cage. One male animal was placed into each cage. All female animals were followed up every other day by a vaginal smear method. Pregnant animals were taken into single cages. From the first day of the pregnancy on, all animals in the experimental group were given 100 mg/kg/day standardized Saint John's Wort extract in 2 ml of distilled water by gavage. Animals in the control group were given 2 ml of distilled water every day from the first day of pregnancy by an orogastric probe. The pregnant animals were allowed to deliver by the normal vaginal route. Immediately after birth, five randomly born pups from each mother in both groups were taken from the cages and included in the experiment (Figure 1). The other offsprings were excluded from the study.

After measuring and recording height and weights, the pups were sacrificed under anesthesia, followed by a laparotomy where the right lobes of the livers were removed and put into 10% neutral buffered formalin.

Histopathological Evaluation

After routine histological follow-up, three sections of 5-6 micron thickness (each section followed by 15 skipped sections) were taken from the liver tissues embedded in paraffin. The sections were stained with hematoxylin-eosin. The stained preparations were evaluated histopathologically and photographed on an Olympus BX50 light microscope. The evaluation was based on two criteria: Microvesicular steatosis and hydropic degeneration. Scoring of the findings was done as follows:

0: No lesion at all

1: Mild damage

2: Medium damage

3: Severe damage

Each criterion was evaluated using all three sections from each animal, and the mean values were reported.

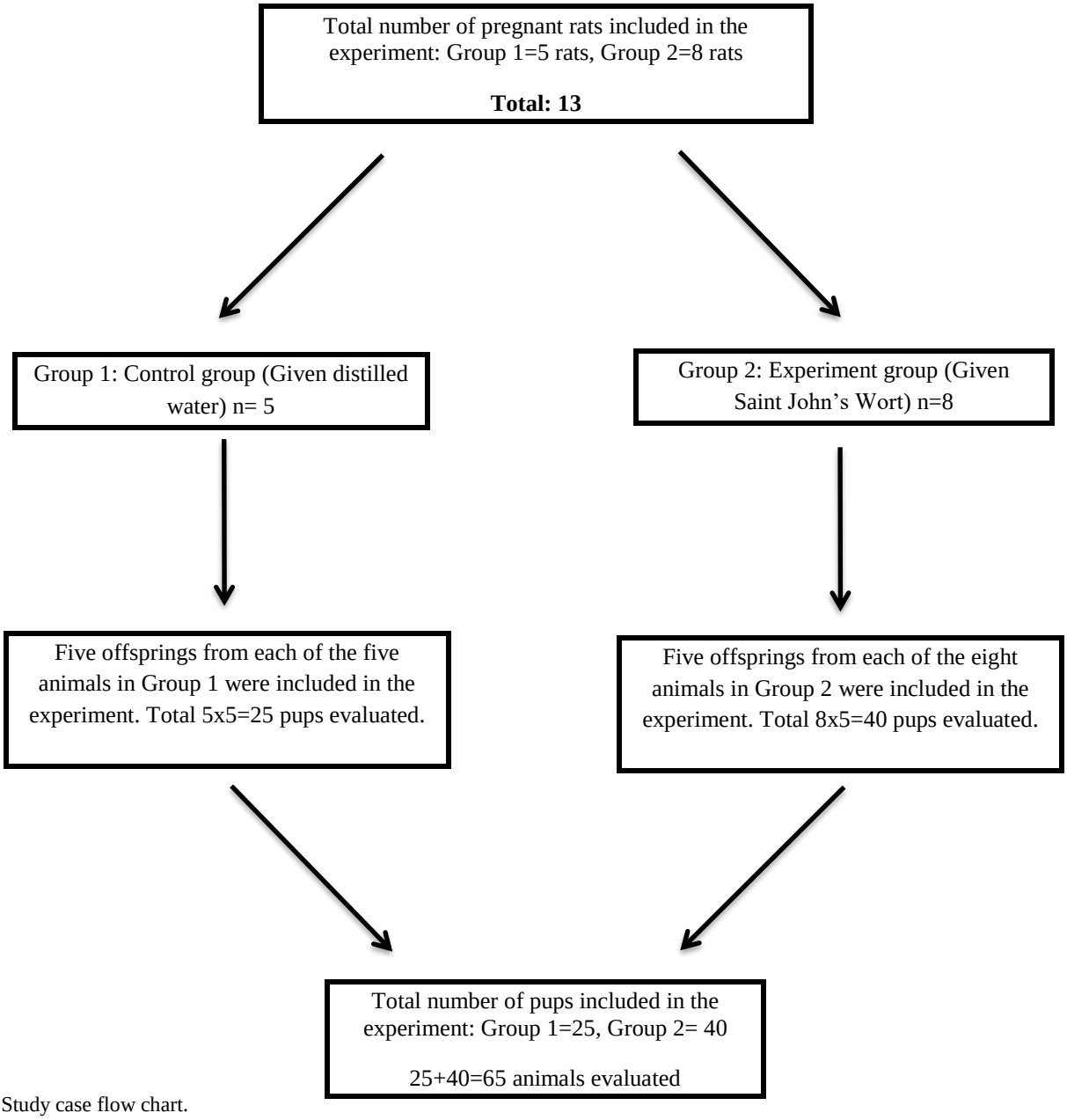

Figure 1. Study case flow chart.

Statistical analysis

Statistical analyzes of the results were done using the SPSS (SPSS Inc., Chicago, IL, USA) 13.0 package program. The results were analyzed using Student t and Mann Whitney U tests. A p value of <0.05 was considered significant.

Results

Clinical Observation

There were no differences in the clinical appearance of the animals in the study and control groups. Also, there was no difference between the offsprings of both groups. The number of puppies born from the rats in the control group ranged from 9 to 15 (mean 11.2), and the number of puppies from the rats in the experimental group ranged from 8 to 15 (mean 8.8). There was no statistically significant difference between the numbers of pups of the two groups ($p = 0.316$).

Histopathological Findings

In the histological sections, a normal liver structure with hematopoiesis in some areas was observed in the liver tissues of the control puppies (Figure 2).

Areas of hematopoiesis were also observed in the tissue sections of the pups in the experimental group. Apart from this, general organ structure was preserved, but microvesicular type of areas with steatosis were widely observed. Besides, frequent hydropic degenerations were observed in the hepatocytes (Figure 3-6).

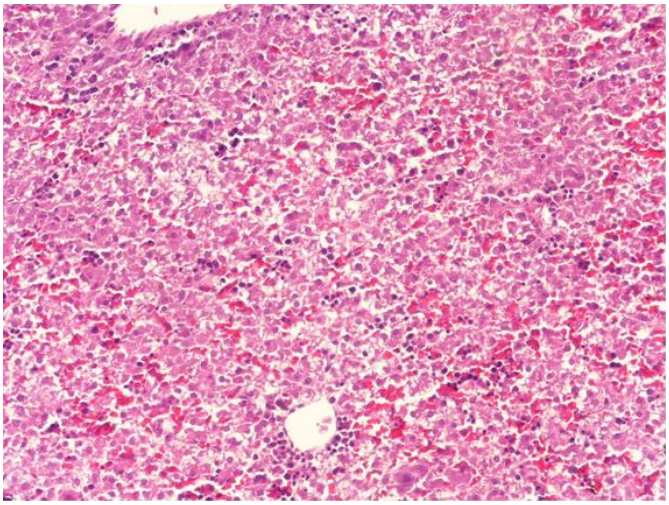

Figure 2. A hepatic section from the control group (10x20 magnification). Normal liver structure and hepatocytes at central vein and surroundings are seen. Also, hematopoiesis could be differentiated in some areas.

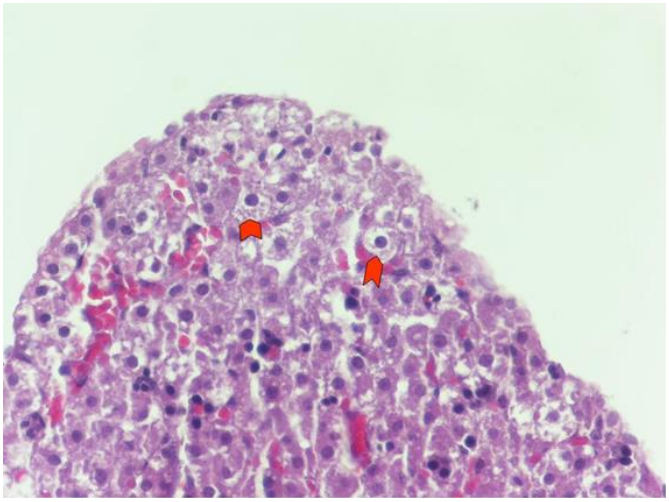

Figure 3. Hepatic section (10x40 magnification) taken from the group given Saint John's Wort. Arrowheads indicate areas of hydropic degeneration.

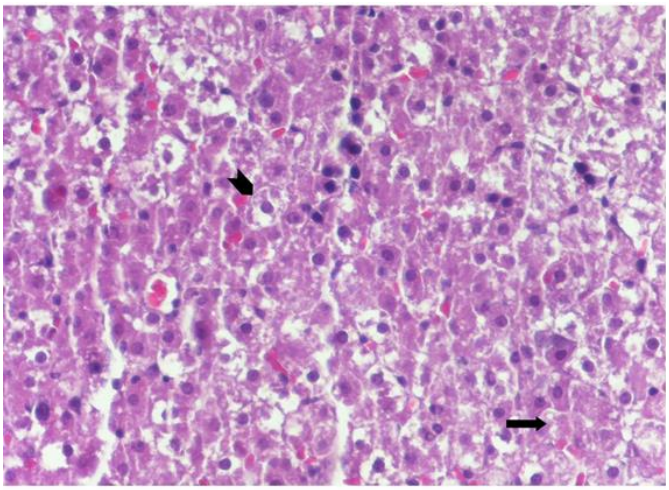

Figure 4. Hepatic section (10x40 magnification) taken from the group given Saint John's Wort. Arrow indicates microvesicular steatosis; arrowhead shows hydropic degeneration.

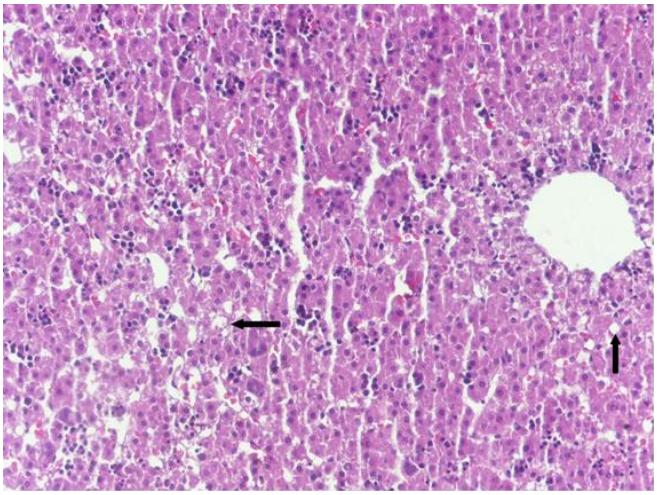

Figure 5. Light microscopic appearance (10x20 magnification) from the group given Saint John's Wort. Arrows indicate areas of microvesicular steatosis. Areas of continuing hematopoiesis are observed.

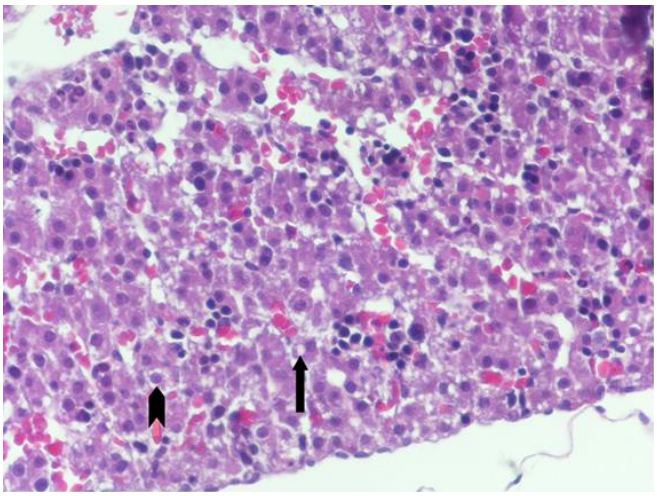

Figure 6. Hepatic section (10x40 magnification) taken from the group given Saint John's Wort. The arrow shows areas of microvesicular steatosis, arrowhead showing hydropic degeneration areas. Occasional hematopoiesis areas are seen.

Histopathological findings of the experimental group were significantly different when compared with the control group ($p < 0.05$) (Table 1).

Table 1. Comparison of histopathological findings of the control and experimental groups (Mann-Whitney U test)

Histopathological findings	Control group (n=25)	Experimental group (n=40)	p-value
Microvesicular steatosis ± SEM	0.067±0.0376	0.782±0.0916	<0.050
Hydropic degeneration ± SEM	0.022±0.0222	1.048±0.1112	<0.050

Evaluation of Growth and Development

When the birth weights and heights of the pups were measured, significantly lower birth weights were found in the experimental group compared to the control group ($p < 0.05$). However, there were no significant differences between the groups concerning heights ($p > 0.05$) (Table 2).

Table 2. Comparison of mean heights and weights of the control and experimental group pups (Student t-test)

Mean values	Control group (n=25)	Experimental group (n=40)	p-value
Mean height (mm±SEM)	40.24±0.230	40.20±0.277	>0.05
Mean weight (gr±SEM)	5.6713±0.05646	5.3436±0.07144	<0.05

Discussion

There are two case reports in the literature about the use of Saint John's Wort in pregnancy. In the first case, except for maternal thrombocytopenia and neonatal jaundice, no significant side effects attributable to Saint John's Wort were observed. In the other case, it was reported that the baby was healthy at birth, with normal birth weight and APGAR scores. Also, the physical examination, laboratory results, as well as the behavioral tests performed on days 4 and 23 were normal [18]. None of the cases discussed in the available literature report low birth weight or growth and developmental issues. In this work, however, offsprings of the rats given the St. John's Wort during pregnancy had significantly lower birth weights compared to the control group. This contradicts the normal birth weights seen in the literature. However, since the results in the available case report belong to a single case, they do not bear strong clinical significance; it could possibly be comparable to our results if observed in a patient group. In our study, the values of 65 pups were examined, and the results were compared statistically. It is known that the data obtained in this way are more reliable than the results of individual cases. Besides, the baby's birth weight in the case report may not be affected because the St. John's Wort was used after the 2nd trimester of the pregnancy. However, in our study, the pregnant rats were exposed to the St. John's Wort right from the diagnosis of the pregnancy throughout the gestation, including the first trimester, the period of essential organogenesis. The low birth weight may be explained by this long exposure period.

In a controlled cohort study of the use of the Saint John's Wort in pregnancy, 54 women who had used this herb during certain periods of their gestation were studied and found that infants born after intrauterine exposure did not have adverse outcomes compared to those who did not receive the herb [19]. Unlike in our study, pregnant women in this study used Saint John's Wort only for a certain period of the pregnancies. In the majority of the patients included in the literature, there is a rather short duration of exposure. However, in our study, the Saint John's Wort was given during the entire pregnancy period from the first day on. This includes both the first trimester of organogenesis and the second and third trimesters of the growth and development. Due to this significant difference, the reported literature may lack findings regarding low birth weight.

A variety of animal studies on the use of the Saint John's Wort during pregnancy are available in the literature. Chan et al. [20] have shown that hypericin, one of the active ingredients of the Saint John's Wort, is teratogenic on rat embryos at clinical doses used for humans. The results of this study are similar to our findings. However, in our current study, the effects of the Saint John's Wort on the liver were determined as hydropic degeneration and microvesicular steatosis, which cannot be considered as teratogenic. The teratogenic effects found by the above-mentioned article were not observed in our study, and it was observed that the development of the offsprings was normal in the physical and intrauterine examination. The conclusions reached by Chan et al. were drawn from studies performed in the cell culture medium. However, in vitro and in vivo effects of a substance can be different. An effect seen in the culture medium may not be observed in an in vivo environment. In some cases, even the opposite may be true. Our results are more appropriate in reflecting the in vivo effects of using the Saint John's Wort. In this regard, we believe that clinical outcomes may be more accurate in reflecting the likely effects.

In a study of Sprague-Dawley rats, Cada et al. [21] found that the Saint John's Wort did not cause behavioral changes in the fetuses. In our study, no behavioral parameters were observed, and the offsprings were sacrificed following postpartum height and weight measurements. In their studies on mouse pups, Rayburn et al. could not show a significant difference in cognitive, behavioral, growth, and physical maturation, but found that the birth weights of male pups were significantly lower than those in the placebo group [22-24], which is similar to our results. However, in our study, the offsprings were not separated by sex, and the results were evaluated together. This difference can be considered as a limitation of our work.

No detailed histopathological analysis has been performed in any of these studies, and the toxicity of the Saint John's Wort taken during pregnancy has not been evaluated at the tissue level. However, the most accurate method for claiming the reliability of using a substance is by revealing its

histopathological effects. The presence of tissue damage indicates that the substance is harmful, and thus, its use is not safe. For this reason, in this study, we gave the rats a standardized concentration of 100 mg/kg/day Saint John's Wort extract from the first day of pregnancy until birth. Immediately after birth, we measured the height and weights of the offsprings to determine whether the herb had any effects on growth and development and whether they had any toxic effects on the fetal liver by subjecting the offspring's liver tissues to histopathological examination.
In our study, when compared with the control group, the pups of the Saint John's Wort-fed rats had statistically significant damage to the liver tissues ($p < 0.05$). This damage was in the form of hydropic degeneration and microvesicular steatosis. In a study conducted at the dose of 100 mg/kg/day, consistent with our study, liver damage was found in the offsprings in the form of serious hepatocyte damage with vacuolization. However, in this study, the application of the Saint John's Wort to the animals was started two weeks before pregnancy and continued during pregnancy and the postpartum 21-days period [25]. In this study, the animals received the Saint John's Wort for a longer duration. In our study, although the concentration of the Saint John's Wort was taken only during pregnancy, the same level of liver damage and liver toxicity findings were observed. Besides, our study tried to model the use of this plant against depressive symptoms during pregnancy. The current literature, on the other hand, includes the use of the plant before pregnancy, as well as during pregnancy and lactation [25].

We observed that the birth heights of the offspring of the mothers who were exposed to the Saint John's Wort during pregnancy did not show a statistically significant difference when compared to the control group, but the birth weights were significantly lower than the control group. In a similar study, the birth weights of the offspring were not different from the control group [25]. In our study, 100 mg/kg/day of the Saint John's Wort was applied during pregnancy, and the offspring had lower birth weights compared to the control group. However, in the literature, even though the animals received the same dose during pregnancy starting from two weeks before gestation, the birth weights were not affected. In this study, three animals were used in each of the experiment and control groups. Having no statistically significant difference between the birth weights of the experimental and control groups may be due to the insufficient number of subjects; we had a substantially higher number of pups (65 pups born from 13 mothers).

In the literature, where pregnant rats received Saint John's Wort at a dose of 36 mg/kg/day during the 9-15th days of the organogenesis period, fetal birth weights of the control and experimental groups were compared, and no statistical difference could be demonstrated [26]. The reason for the Saint John's Wort not influencing the birth weights of the offspring might be related to the quite low dose compared to the 100 mg/kg/day dose used in our study and Saint John's Wort being applied for only 7 days during pregnancy; in our study, the Saint John's Wort herb extract was used throughout the pregnancy until birth. The reason for this was to investigate the effects of using this herb against the symptoms of depression during pregnancy, especially in the last trimester.

In this study, we tried to demonstrate histopathologically the toxic effects of using Saint John's Wort in pregnancy on the fetal liver tissue. However, we did not investigate the effects of this herb on other tissues of the fetus. In particular, we consider having not included studying the toxicity in the kidney and lung tissues as a limitation of this study. Besides, the fetal liver damage was histopathologically proven but not supported biochemically. The lack of studying biochemical liver function tests is another limitation of our study.

Conclusion

In conclusion, the present study showed that feeding rats with Saint John's Wort during pregnancy caused low birth weight in the fetus. It was also demonstrated histopathologically that the Saint John's Wort caused toxic damage to the liver tissue. Histopathological changes were observed as microvesicular steatosis and hydropic degeneration. It is essential for the physicians (especially the primary care physicians) to be aware of the risks and evaluate the use of this herb during pregnancy and to raise the awareness of the pregnant women during routine follow-ups. Further studies are needed to determine the safety of using the Saint John's Wort during gestation and study its effects on all organ systems of both the mother and the fetus.

Conflict of interest: None
Financial support: None

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