IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 13, Issue 5 Ver. IV (Sep – Oct 2018), PP 30-36
www.iosrjournals.org

Evaluation of toxicity in rats of *Ruta chalepensıs* L. extracts Growıng in Iraq

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Abstract: *Evaluate the acute and chronic toxicity of Ruta Chalepensis aerial part aqueous extract used in folk medicine in Iraq in Albino Wistar male and female rats. The study of chronic toxicity at the doses 100, 300 and 600mg/kg body weight in male and female rats for 90 days, recorded no mortality. Treated animals showed a normal weight change compared with control. The parameters of male fertility showed a significant decrease in the weight of testis, epididymis and seminal vesicle as well as a reduction in the number and the motility of spermatozoids at treated groups by the doses 300 and 600 mg/kg body weight compared to control group.*
Key words: *Ruta Chalepensis L.,acute toxicity, chronic toxicity, testis*

Date of Submission: 10-10-2018 Date of acceptance: 26-10-2018

I. Introduction

Medicinal plants have important contributions in the healthcare system. Use of herbal medicines represent a long history of human interactions with the environment.

Plants used for traditional medicine contain a wide range of substances that can be used to treat chronic as well as infectious diseases. A number of modern drugs currently in use have been obtained through medicinal plants [1].

Despite the profound therapeutic advantages possessed by some of the medicinalplants, some constituents of medicinal plants have been found to be potentially toxic,mutagenic, carcinogenic and teratogenic [2]. This raises concern about the potential toxiceffects resulting from the short-term and long-term use of such medicinal plants.

Therefore, evaluating the toxicity effects of any medicinal plants extracts intended to beused in humans and animals is of greatest significance [3].

Ruta chalepensis L. (family: Rutaceae), commonly known as "fringed rue", is a perennial herb (*ca.* 80 cm tall), Its flowers are cymes with 4-5 sepals, 4-5 petals, 8-10 stames and a superior ovary. *Ruta chalepensis* is a perennial herb that widely distributed in the Mediterranean area1 and also was introduced in America after the Spanish conquest [2]. It is one of the most frequently used plants for medicinal purposes [3,4]. Oil glands, that are principally present in leaves, give its strong deterrent odors [5,6]. *Ruta chalepensis* pharmacological properties, attributed to the high content of alkaloids [7-9], such as furocoumarins7, coumarins9 and furoquinolone alkaloids [10], flavonoids, phenols, amino acids and saponins found in the leaves and stems of the plant [11]. *Ruta Chalepensis* is used, in the traditional medicine for the treatment of various disorders, as analgesic and antipyretic and for the treatment of rheumatism and mental disorders[1]. Also it has emmenagogue, abortificient, antihelmintic and spasmolytic effects[12] as well as its potency as anti-infamatory13, antihelminthic14, antifungal15, antifertility, anticonvulsant and sedative[16,17]. In children, infused *Ruta chalepensis* leave extract has been used for treatment of convulsion and other nervous disorders. In Africa, the aqueous decoction of the leaves is used for the treatment of fever [4]. More than fifty chemical compositions of *Ruta chalepensis* essential oil were studied by many research teams in Iran18, Greece19, Turkey20 and India [21,22].

II. Materals and Methods

- **Preparation of plant extracts**

The aerial parts of the plant material were cleaned with tap water, dried in shade atroom temperature for 2 weeks and ground into fine powder using an electric grinder.

- **Aqueous extract**

The aqueous extract was prepared according to the method described by Mbiantcha[23], with some modifications. Briefly, 100g of *Ruta chalepensıs* L. powder wasmixed with 1L of boiled distilled water (100 °C) at room temperature during 72h, themixture was filtered using Wattman filter paper n°3 and then evaporated in rotary vacuumevaporator

2.3 Animals

Males and females of *Albino Wistar* rats. These animals were kept in theanimal house, at a temperature of 25°C and a natural photoperiod cycle. The animals werehoused in plastic cages (5 rats per cage) and had free access to standardcommercial diet and tap water.

- **Anımal groping and extract admınıstratıon;**

Albino Wistar rats of both sexes weighing between 149 and 200 g were divided intofour groups of 10 rats each (5 females and 5 males). The aqueous extract dissolved indistilled water, was administered daily by gavage for 90 days to groups I to IV (doses of 0,100, 300 and 600 mg/kg, respectively). The animals were observed for signs of toxicityand mortality throughout the experimental period. At the end of the treatment, animalswere fasted overnight, but allowed access to water ad libitum. They were subsequentlyanesthetized with diethyl ether and blood samples were obtained by retro-orbital puncture[24] and collected in two tubes. The first one containing EDTA and it wasprocessed immediately for hematological parameters analysis. The second containingheparin and it was centrifuged at 4000g at 4°C for 15 min to obtain serum (stored at −20°Cuntil analysis). The organs (tests, epididymis and ovaries) were weighed and fixed in 10 % formalin for histopathological examination.

III. Result and Discussion

Effect of *Ruta chalepensıs* L. aqueous extract on Fertility

3.1 Sperm suspension

The epididymis of each rat was placed in 1 mL of ringer buffer, the spermatozoawere obtained by making small cuts in caudal epididymis and diluted by adding 9 mL ofringer buffer (1/10) and then incubated at 37°C for 10 minutes. The sperm suspension wasused for analysis of motility and counts.

3.2 Sperm count and motility

A sample of sperm suspension was taken and the number of sperm counted using ahaemocytometer under the light microscope at a magnification of x40. Four squares werecounted in triplicate. The count was expressed as 2500/mm of suspension. Sperm motility(%) was also assessed immediately by counting both motile and immotile spermatozoa atthe magnification of x40 and calculated by the formula:

Number of motile sperm x 100/total number of motile and immotile sperm.

- **Histopathological examination**

The treated and control rats' organs were taken out. They were weighed and examined for the evidence of gross lesions. Similar samples were fixed in 10% formalin solution, dehydrated ingraded (70-90%) alcohol, cleared in xylene, and placed and embedded in paraffin wax.

To perform histology of tissues, 5-6 µm sections were prepared using Microtome (Leica, RM 2145). These sections then deparaffinated in xylene, passed through 70% to 90% alcohol, and stained with hematoxylin and eosin (H&E). The slides prepared by this process was observed under light microscopy [25] .

- **Chronic toxicity**

In chronic toxicity study, rats were divided into 4 groups of 10 animals (5 femaleand 5 male). The rats were treated with the aqueous extract of *Ruta chalepensıs* L. at threedoses (100, 300 and 600 mg/kg of body weight/day) for 90 days, while the control groupwas given only the distilled water.

No toxicity signs or death were recorded during the 90 consecutive days of treatment *via* oral route with *Ruta chalepensıs* L. aqueous extract at doses of 100, 300 or 600 mg/kg of body weight.

- **Effect of *Ruta chalepensıs* L. aqueous extract on rats' body weight**

Changes in body weight are an indicator of adverse effects of drugs and chemicalsand it will be significant if the body weight loss is more than 10% from the initial bodyweight occurred [26,27].

The results of body weight of control and treated rats are presented in figure 1 andfigure 2 . Statistically, no significant difference was noted in the body weight between thecontrol and any of treated groups (1-4) at any time period.

Fıguer (1) changes in body weight of male rats after chronic oral treatment with

Fıguer(2) changes in body weight of male rats after chronic oral treatment with Effect of *Ruta chalepensıs* L. aqueous extract on sperm count and motility.

The sperm count in control group was 14.21 ± 2.99 x 2500 sperm/mm3, in group I 8.66 ± 2.22 x 2500 sperm/mm3, in group II 5.5 ± 0.04 x 2500 sperm/mm3 and in group III 1 ± 0.00 x 2500 sperm/mm3. Whereas the motility in control group was 63.73 ± 2.27 (%), in group I 60.00 ± 2.09 (%), in group II 19.42 ± 4.25 (%) and in group III 0.00 ± 0.00 (%) (Table 1). In Ruta chalepensıs L. aqueous extract treated rats the epididymidal sperm parameters showed evidence of dose dependent toxicity. The sperm count and motility were significantly decreased in group II and group III.

Table 1. Effect of *Ruta chalepensıs* L. aqueous extract on sperm count and motility

Control	Group I	Group II	Group III	Group IIII
	(0 mg/kg)	(100mg/kg)	(300mg/kg)	(600mg/kg)
Count (2500/mm3)	14.21± 2.99	8.66±2.22	5.5±0.04**	1±0.00***
Motility (%)	63.77±2.27	60.00±2.09	19.40±4.25***	0.00±0.00***

Values are presented as means ± SD; ** P < 0.01, *** P < 0.001 compared with control

- **Effect of *Ruta chalepensıs* L. aqueous extract on rats' organs histology**

there are no histological changes observed in ovary in all treated groups compared with control group (Figure 3).

Histological examination of the testes of control group showed normal histological structure of the seminiferous tubules associated with complete spermatogenic series as demonstrated in figure (4 A). The testes of rats given 100 mg/kg of body weight of *Ruta chalepensıs* L. aqueous extract had similar histological appearance as the control rats (Figure 4B)**,** and showed active spermatogenesis, however, the testes of the rat treated with 300 and 600 mg/kg of body weight of *Ruta chalepensıs* L. revealed degeneration of seminiferous tubules with absence of sperm in tubular lumen as shown in figure (5A) and figure (5B). For the epididymis of control group and the group treated by 100 mg/kg of body weight showed normal tubules that contained spermatozoa in the lumen (Figure 6A and B). Whereas, the treatment with the doses 300 and 600 mg/kg of body weight caused damage in epididymis tubules and absence of sperm (Figure 7A and B).

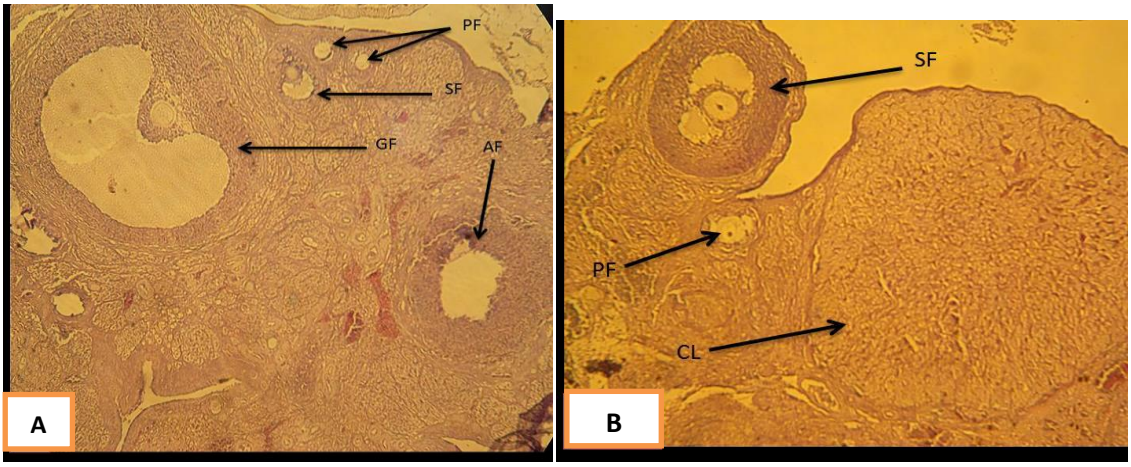

Figure 3: Histological sections of Ovary of control group (A) and group 1 (B) treatedwith 100 mg/kg bw of *Ruta chalepensis* L. aqueous extract after 90 days of treatment showingnormal structure. PF: primary follicle ; SF: secondary follicle ; GF: grafian follicle ; atresiafollicle ; CL : corpus luteum. (HE X 200)

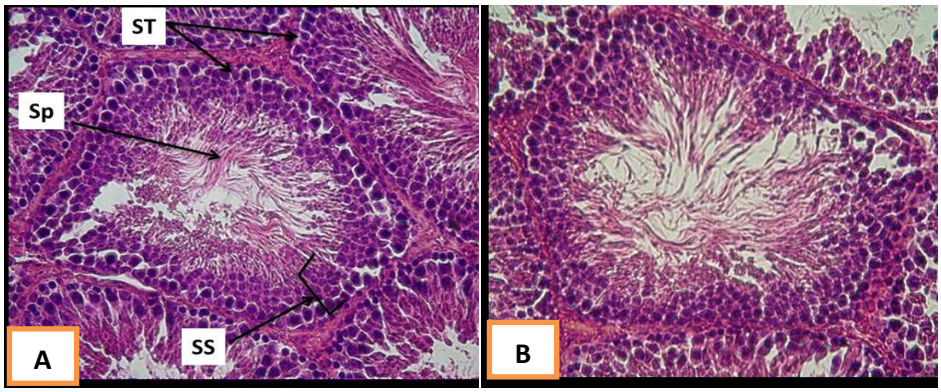

Figure 4: Histological sections of testes of control group (A) and group 1 (B) treatedwith 100 mg/kg bw of *Ruta chalepensis* L. aqueous extract after 90 days of treatment showingnormal histological structure of the semiferous tubules associated with completespermatogenic series and spermatozoa in the lumen. ST: seminiferous tubules; Sp: sperm;SS: stages of spermatogenesis. (HE X 200)

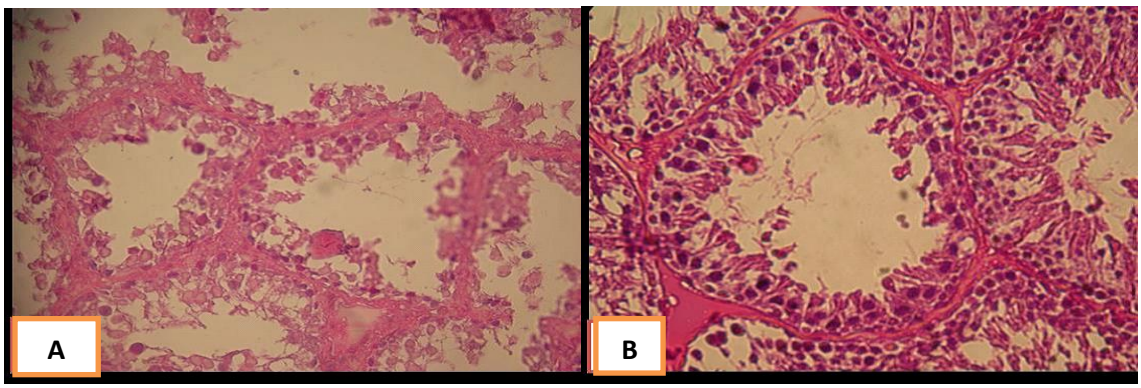

Figure 5: Histological sections of testes of group 2 (A) and group 3 (B) treated with300 mg/kg and 600 mg/kg bw respectively of *Ruta chalepensis* L. aqueous extract after 90days of treatment showing degeneration of seminiferous tubules with absence of sperm intubular lumen. (HE X 200)

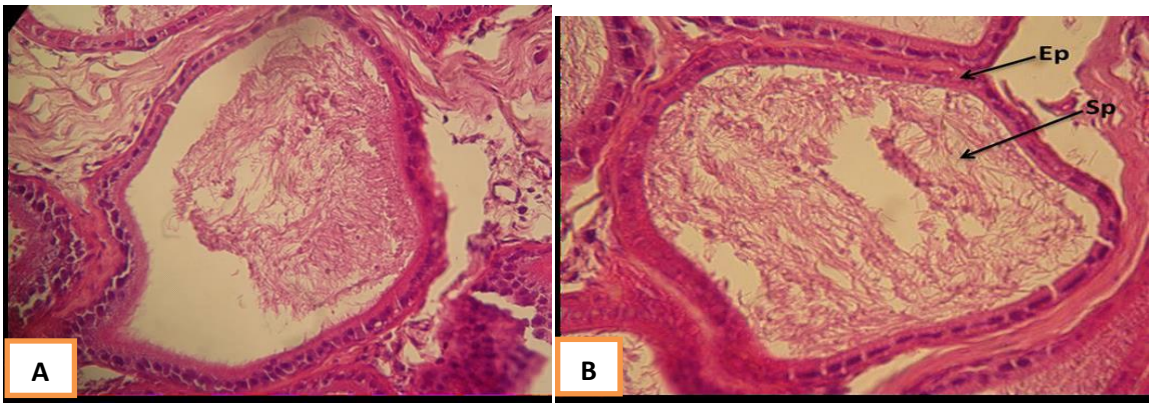

Figure 6: Histological sections of the epididymis of control group (A) and group 1 (B)treated with 100 mg/kg bw of Ruta chalepensis L. aqueous extract after 90 days of treatmentshowing normal tubules that contained spermatozoa in the lumen. Ep: Epethelial cells; Sp:Sperm. (HE X 200)

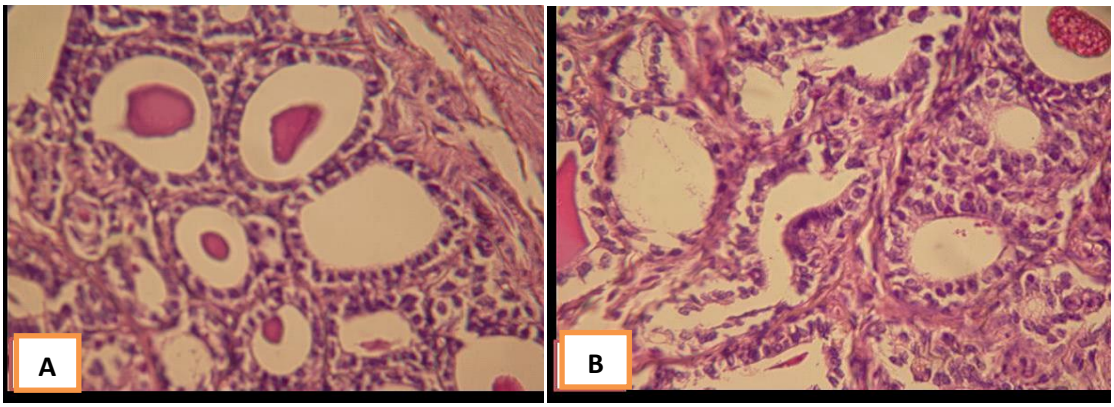

Figure 5: Histological sections of the epididymis of group 2 (A) and group 3 (B)treated with 300 mg/kg and 600 mg/kg bw respectively of Ruta chalepensis L. aqueousextract after 90 days of treatment showing damage in epididymal tubules and absence ofsperm. (HE X 200).

IV. Discussion

Medicinal plants have been in use all over the world to treat various diseases including inflammation, heart diseases, cancer, etc. Today the large numbers of drugs in use is derived from plants, which are rich in secondary metabolites and essential oils of therapeutic importance. The important advantages claimed for therapeutic uses of medicinal plants in various ailments are their safety besides being economical, effective and their easy availability [28]. In rats receiving the Ruta chalepensis L. aqueous extract orally at doses of 100, 300 or 600 mg/kg during 90 consecutive days, there was no significant change in the body weight in the treated groups compared to the control group. Changes in body weight have been used as an indicator of adverse effects of drugs and chemicals [29]. Since, no significant changes were observed in the body weight, in the treated groups compared to that of the control group, it suggested that at the oral doses administered, Ruta chalepensıs L. aqueous extract had no effect on the growth of rats. Generally, the alterations of body weight gain and internal organ weights of mice would reflect the toxicity after exposure to the toxic substances [30]. Organ weight is an important index of physiological and pathological status in animals. The relative organ weight is fundamental to diagnose whether the organ was exposed to the injury or not [31]. In this study, no significant changes were observed in the internal organ weight after the 90 days' period, except a significant decrease in testis, epididymis and seminal vesicle in groups treated by the doses 300 and 600mg/kg when compared to the control group. In addition, there is no changes were observed in gross observation of organs of both control and treated groups. In the present study, a significant weight reduction was seen in the testes, epididymis and seminal vesicle in the doses 300 and 600 mg/kg when compared to the control group. The weight reduction was dose dependent. These results are similar to those obtained by Khouri and EL-Akawi [32], which suggest that the administration of aqueous extract of Ruta graveolens L. at a dose of 500 mg/kg body weight for 60 days induces a significant decrease in the weight of reproductive organs ($P<0.01$) when compared to control. But, do not agree with the results obtained by Al Qarawi [33] which suggest that the oral administration of an aqueous extract of the leaves of Ruta chalepensis in daily oral doses of 0.5 g, 1.0 g and 2.0 g for 30 days caused an increase of the testicular and epididymis weights. Generally, the reductions in internal organ weight are simple and sensitive indices of toxicity after exposure to toxic substances [27]. The significant reduction of testis weight is known to be mostly related to number of spermatids and spermatozoa present in the tissue [34]. The significant reduction in the weight of reproductive organs indirectly support the reduced availability of androgen [35] . It is known that the accessory sex organs are androgen dependent target organs and manifest differential sensibility to androgens for maintenance of their structure and function. It is also known that, any change in circulating androgens would affect the internal microenvironment of epididymis and thereby lead to alteration in sperm motility and metabolism [36]. Androgen deprivation not only suppresses spermatogenesis, leading to low sperm concentration, but also alters the epididymal milieu which renders it hostile for maturation and survival of the spermatozoa [37,38]. Testosterone, an important androgen, plays a pivotal role in maturation, spermatogenesis and the maintenance of 100 accessory sex organs [39]. The structural and functional integrity of reproductive tissues depends on the circulating androgen [40]and therefore, any small change in testosterone content may result in reductions in the weights of the reproductive organs. Sperm characteristics are important reproductive indices as they account for male fecundity. The aqueous extract at the doses of 300 and 600 mg/kg body weight produced a significant reduction in the sperm count and motility. Two possible hypotheses may be proposed to explain this reduction. One hypothesis is that the principles active of the extract may alter the pituitary gonadotropins hormones: luteinizing hormone(LH) and follicle stimulating hormone (FSH) ([41]. It is well known that the weight, size and the Secretary function of testes, epididymis and seminal vesicles are

closely regulated by androgens hormones [42]. The production of the sperm cells (spermatozoa) and testosterone in the testis are mainly regulated by the follicle stimulating hormone and Luteinizing hormone, which are released from the interior pituitary [43]. FSH stimulates spermatogenesis in the sertoli cells, while LH stimulates the production of testosterone in leydig cells of the testis [44]. Low levels of these hormones decrease endogenous testosterone secretion from the testis depriving developing sperm of the signal required for normal maturation and also it suppress testicular steroidogenesis and spermatogenesis [45] since the pituitary-testicular axis is a central regulatory conduit for testicular function that culminates in the production of spermatozoa [46]. Besides hormonal alteration, the alternative hypothesis is that the principles active may induce oxidative stress in testicular tissue and stored germ cells leading to generation of free radical products, as they exert a detrimental effect on spermatogenesis [47]. The histological examination is the golden standard for evaluating treatment related pathological changes in tissues and organs [48]. In the present study, histopathological evaluation of chronic oral administration of Ruta chalepensis L. indicated that the aqueous extract did not cause toxicity towards the organs as there was no structural damage to the organs of ovary of the rats.

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Mustafa A. K. AL-Taie. "Evaluation of toxicity in rats of Ruta chalepensıs L. extracts Growıng ın Iraq." .IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 13.5 (2018): 30-36