Pharmacologia 3 (11): 598-604, 2012
ISSN 2044-4648 / DOI: 10.5567/pharmacologia.2012.598.604


# Acute and Subacute Toxicity Studies of Alkaloids of Seeds and Synthetic Alkaloids of *Datura stramonium* in Female Rats

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**Abstract:** The effects of acute, subacute administration of alkaloids atropine and scopolamine, the main constituents of the active principle of *Datura stramonium,* with toxic properties, were studied in female Albino-Wistar rats. After acute intraperitoneal administration of dose 100 mg $kg^{-1}$ (≈1/4 $DL_{50}$) of total alkaloids to the seeds of *D. stramonium*, there were no remarkable changes in general appearance and no deaths occurred in any experimental group. After 24 h a significant reduction was observed in total alkaloids of seeds. The Red Blood Cells (RBC), Hematocrit (HCT) and Hemoglobin (HGB) did not show significant changes in the treated groups. There were no statistical differences in Glutamic-Oxaloacetic Transaminase (GOT), Glutamic-pyruvic Transaminase (GPT) and Alkaline Phosphatase (ALP) observed between groups. Histological examination of liver showed no histopathological changes. Subacute study for four weeks showed no resulting mortality or signs of toxicity. The body gain and relative weight of organs showed no significant changes. These doses of synthetic alkaloids (5.2 mg $kg^{-1}$ of atropine and 2.6 mg $kg^{-1}$ of scopolamine) did not produce significant changes of hematological parameters (RBC, HBG and HCT) and biochemical (GPT, GOT and ALP) in comparison with the control group. Alkaloids of *D. stramonium* showed no significant toxicity in female rats.

**Key words:** Toxicity, *Datura stramonium,* alkaloids, atropine, scopolamine, female rat

## INTRODUCTION

*D. stramonium* L. is a member of the family solanaceae. It is commonly known as jamestown weed, jimsonweed, thorn apple, angel's trumpet and devil's trumpet (Forrester, 2006). In Algeria, this plant is locally known as "Sikrane" and is prevalent in North of country, usually matures between May and October (Bouzidi *et al*., 2002). *D. stramonium* is a hallucinogenic plant, widely found in urban and rural areas (Bouziri *et al*., 2011). Datura is used as a drug by adolescents and young people around the world (Birmes *et al*., 2002; Chan, 2002). It contains toxic anticholinergic alkaloids atropine, scopolamine and hyosciamine (Sever and Cekin, 2007; Miraldi *et al*., 2001) which are a muscarinic acetylcholine antagonists, reducing cholinergic neurotransmission in both the autonomic and central nervous systems (Parrott, 1986) and caused warm, flushed skin, dry mouth, mydriasis, delirium and hallucinations, tachycardia and urinary retention (Rodgers and Von Kanel, 1993).

The *D. stramonium*has been involved in accidental poisoning of animals of farm livestock and poultry. The plant was mistakenly gathered together with corn intended for animal feeds (Nelson *et al*., 1982; Naude *et al*., 2005; Kara *et al*., 2009; Botha and Penrith, 2009; Guitart *et al*., 2010) and companion animals (Tostes, 2002; Berny *et al*., 2010).

Moreover, few experimental studies in laboratory animals have been performed to evaluate the effect of this plant and its alkaloids (Dugan *et al*., 1989; Gidado *et al*., 2007; Adekomi *et al*., 2011). Therefore, a study was designed to find the effect of this plant and its alkaloids on some important parameters in female rats.

## MATERIALS AND METHODS

**Plant material:** Seeds of *Datura stramonium* were collected in south Setif (east Algeria) between August and September. The seeds were stored at room in dry place. After drying, the seeds were kept in tightly-closed containers prior to use (Fig. 1, 2).

**Extraction of total alkaloids:** Hundred gram of Air dried powdered of seeds was defatted with petroleum ether under reflux and then the seeds were witted with150 mL of $NH_4OH$ (25%, m $m^{-1}$) for 4 hours and were extracted to exhaustion with $CHCl_3$ using a soxhlet apparatus for 6 h. The organic extract (containing free alkaloids+lipophilic

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Fig. 1: *D. stramonium* L. in period of flowering and fruiting

Fig. 2: Fruit and seeds of *D. stramonium*

impurities) is then shaken three times with 150 mL aqueous sulphuric acid (2%, m $m^{-1}$). The acid extracts (alkaloids salts) are treated three times with 50 mL $NH_4OH$ (25%, m $m^{-1}$) to pH 10 to liberate the free alkaloids which are separated by extraction with 150 mL $CH_2Cl_2$ and then dried with $Na_2SO_4$ and concentrated to dryness under reduced pressure to obtain crude alkaloids (Bruneton, 1999). The yield of this extract was approximately 0.089±0.02 % (w/w).

**HPLC analysis:** A Pyeunicam HPLC was used to quantify atropine and scopolamine in total alkaloids of *D. stramonium* seeds. The HPLC system consisted of a isocratic pump, a rheodyne injector equipped with a 20 µL sampling loop and photodiode array detector. Separation was achieved by a Varian/Chrompack column $C_{18}$ (125×4 mm i.d, particle size 5 µm) preceded by a guard column, at temperature 35°C. The mobile phase (delivered at a flow rate of 1 mL $min^{-1}$) consisting of acetonitrile-phosphate buffer (pH 3.8) (15/85, v/v), was filtered through a 0,45 µm membrane and degassed before use, according to method with some modifications (Kirchhoff *et al*., 2004).

**Experimental animals:** Male Albino-Wistar rats weighing between 200-250 g were obtained from animal center of Pasteur's Institute (Algiers-Algeria).

Rats were housed in hanging transparent plastic cages (55×33×19 cm) in the animal room of faculty of sciences University Ferhat Abbas Setif Algeria and acclimated for 3 weeks prior to experiment. The litter was renewed every 3 days. They were fed with a standard pellet and tap water *ad libitium.* All animals were kept in standard environmental conditions (temperature 20-25°C and 12 light/12 h dark cycle). Each rat was identified by body marks using 1% picric acid solution. All experimental procedures were conducted in accordance with the guide for care and use of laboratory animals and in accordance with the scientific council of the faculty of natural sciences and life of the university Ferhat Abbas, Setif-Algeria.

**Preparation of drugs:** The drugs were dissolved in 100 µL of ethanol and diluted with normal sterile saline water.

**Acute toxicity:** Two groups of 10 Wistar albino rats were given single dose of 100 mg $kg^{-1}$ (≈1/4 $DL_{50}$) body weight of alkaloids by intraperitoneal route (but not lethal dose to try to investigate the target organs) (Antov *et al*., 1991).

The control group (10 rats) received saline water with few drops of ethanol at the same volume.

Animals were observed and recorded systematically 1, 2, 3, 4, 5 and 6 h and daily after test substance administration. The visual observations included changes in skin and fur (hair), eyes and mucous membranes and also respiratory, circulatory, autonomic and central nervous system.

The (group I) was sacrificed after 24 h of treatment; and the (group II) after 5 days (see later).

The maximum acute liver toxicity is expressed at day 5 (Szymanowicz and Danel, 2005).

In humans after acute poisoning by *D. stramonium*, hospitalization and recovery takes between 1-5 days (Bouzidi *et al*., 2002).

**Subacute toxicity:** A separate was conducted to evaluated the subacute toxicity of sulfate atropine and bromide scopolamine (were obtained from Fluka-USA) on one group of 10 rats.

The alkaloids (sulfate atropine et bromide scopolamine) were dissolved in 100 µL alcohol and then diluted withnormal sterile saline water and administered daily by intraperitoneal route at dose 5.2 mg $kg^{-1}$ sulfate atropine and 2.6 mg $kg^{-1}$ bromide scopolamine for 4 weeks while control group (10 rats) was given saline water with alcohol at the same volume. The animals were observed

daily for abnormalities and the body weights were recorded at weekly intervals.

At the end of experiment, the animals were examined and sacrificed under the same conditions as described above the acute toxicity.

At the end of all experimental periods, animals were anaesthetized with urethane at the dose 760 mg $kg^{-1}$. Two kinds of Blood were obtained from the retro-orbital vein: a sample for hematology containing ethylene diaminetetraacetic acid with apparatus MEDONIC (Beckman Coulter-USA) and sample for serum and used for measurement of activities Glutamic-oxaloacetic Transaminase (GOT), Glutamic-pyruvic Transaminase (GPT) (using commercial Kits-SGM Rome-Italy) and Alkaline Phosphatase (ALP) (using commercial Kits-CYPRESS DIAGNOSTIC Langdrop-Belgium) with apparatus TECHNICON RA-1000-USA. After blood collection, the animals were sacrificed by cervical dislocation.

After autopsy, all tissues were examined grossly and major's organs (liver, brain, heart, kidneys, Spleen and lung) were weighted. The relative organ weight (weight of organ as a proportion of the total weight of each rat) was calculated and compared with the value of the control.

Tissues from liver of all animals were fixed in 10% buffered formalin solutions then embedded in paraffin and cut with a microtome set at 5 μm, stained with hematoxylin and eosin and examined by light microscopy.

**Statistical analysis:** The statistical significance of differences between means was calculated using one-way ANOVA followed by Tukey's test for multiple comparisons with control group at *$p \leq 0.05$.

## RESULTS

**HPLC chromatography assays:** Representative chromatograms for tropane alkaloids are shown in Fig. 3. under chromatographic conditions used. The retention times for scopolamine and atropine were 9.05 and 16.11 min, respectively. The concentrations of atropine and scopolamine were 4 and 2 mg/100 g of *D. stramonium* seeds, respectively.

**Acute toxicity study of total alkaloids:** The results of the study of animals administered with single dose of 100 mg $kg^{-1}$ body weight of total alkaloids did not show any toxic symptoms such as paralytic, ataxic, lacrimation, laboured breathing or death, immediately after injection or at the end of 5 days.

There were no statistically significant differences in average body weight of the control group and total alkaloids-treated groups during the acute toxicity but significant differences were detected in the weight gain of female (control 12.50±6.55 g; experimental group 5th day 4.6±3.95 g) rats treated with thesynthetic alkaloids, as compared to control group (Table 1).

Table 1: Effect of acute administration of *D. stramonium* (100 mg $kg^{-1}$) on body weight of female rats

| | Body weight (g) | | |
|---|---|---|---|
| Groups | 1st Day | 5th Day | Difference |
| I | 213.3±18.31 | | |
| II | 215.4±9.680 | 235.2±8.430 | 4.6±3.95* |
| Control | 210.2±20.43 | 222.7±19.11 | 12.5±6.55* |

Values are Mean±SD, Significantly different at $p<0.05$

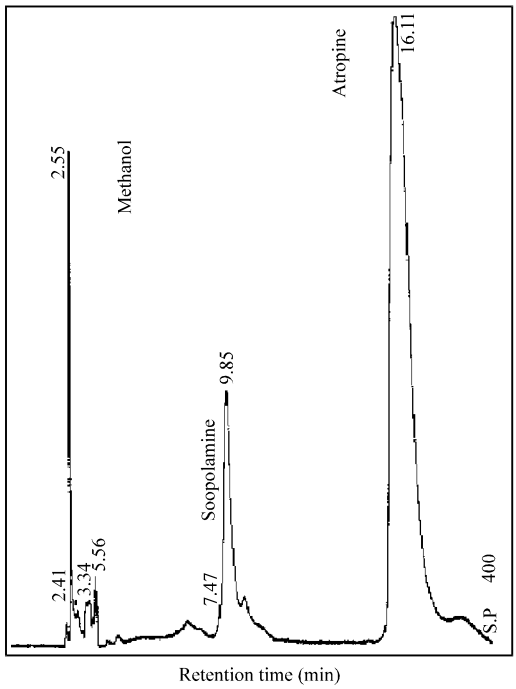


Fig. 3: HPLC chromatogram of the total alkaloids from the seeds of *D. stramonium*. Varian/Chrompack column $C_{18}$. The mobile phase; 85 % phosphate buffer, 15% acetonitrile, flow rate 1 mL $min^{-1}$, pressure 140 bar, 35°C temperature and 210 nm wavelength

The effects of total alkaloids of *D. stramonium* seeds on relative organ (liver, lungs, kidney, heart, brain, testis and spleen) weights are presented in Table 2. There were statistically significant decreases in the relative organ weight of liver of the treated rats of the first group (sacrificed after 24 h).

The haematological parameters of the rats treated with total alkaloids are presented in Table 3. The RBC, RDW (red cell distribution width), HCT, HGB and WBC (white blood cells) were significantly higher in the control group than the treated groups (Table 3).

Table 2: Relative organ weights of female rats treated with 100 mg $kg^{-1}$ of *D. stramonium*

| | Organ weight | | | | | |
|---|---|---|---|---|---|---|
| Groups | Liver | Brain | Kidney | Lungs | Heart | Spleen |
| Control | 0.0381±0.00456 | 0.00853±0.000970 | 0.00734±0.001070 | 0.00967±0.00241 | 0.00393±0.000298 | 0.00469±0.000767 |
| I | 0.0342±0.00239* | 0.00858±0.000538 | 0.00730±0.001000 | 0.00764±0.00565 | 0.00391±0.000295 | 0.00447±0.000593 |
| II | 0.0398±0.00282 | 0.00891±0.000645 | 0.00702±0.000585 | 0.00738 ±0.00155* | 0.00390±0.000332 | 0.00477±0.000766 |

Values are Mean±SD, *Significantly different at $p<0.05$

Table 3: Effect of acute administration of *D. stramonium* (100 mg $kg^{-1}$) on some hematological parameters in female rats

| Group | HGB (g $L^{-1}$) | WBC ($10^3$ $mm^{-3}$) | MPV | PLT ($10^3$ $mm^3$) | HCT (%) | RDW | MCV | RBC ($10^6$ $mm^{-3}$) |
|---|---|---|---|---|---|---|---|---|
| Group control | 14.350±0.43 | 10.37±1.04 | 7.29±0.17 | 464.12±51.390 | 43.71±2.06 | 13.18±1.06 | 54.06±2.06 | 8.10±0.46 |
| Group sacrificed after 1 day | 12.10*±0.57 | 10.02±1.60 | 6.6a±0.25 | 411.78±37.670 | 34.62±1.71* | 12.03 ±0.85* | 53.15±1.91 | 6.51±0.30* |
| Group sacrificedafter 5 days | 13.220±1.00* | 9.53±2.460 | 7.28±0.27 | 536.87±136.62 | 38.54±3.95* | 14.00±0.99 | 54.18±0.6 | 7.11±0.72* |

Values are Mean±SD, *Significantly different at $p<0.05$, RBC: Red blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, HCT: Hematocrit, PLT: Platelets, MPV: Mean platelet volume, WBC: White blood cell, HGB: Hemoglobin

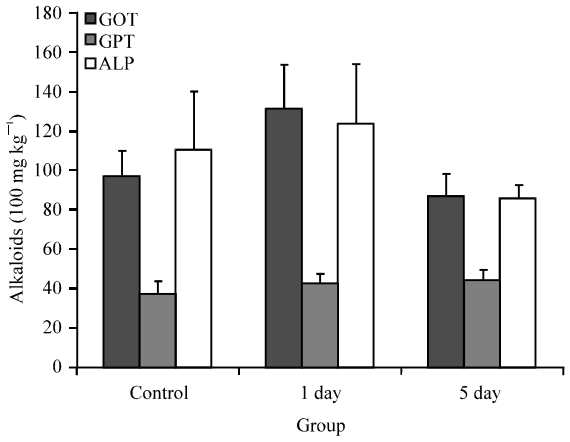


Fig. 4: Effect of acute administration of total alkaloids of seeds of *D. stramonium* (100 mg $kg^{-1}$) on some biochemical parameters in female rats, Values are Mean±SD, vertical line on each bar indicates the standard error

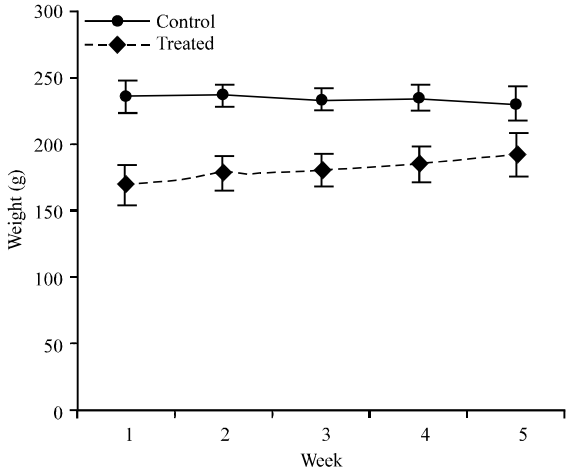


Fig. 5: Effect of subchronic administration of synthetic alkaloids on body of male rats, Values are Mean±SD

The results of the indices of liver function GOT (glutamic-oxaloacetic transaminase), GPT (glutamic-pyruvic transaminase) and ALP (alkaline phosphatase) are given in Fig. 4. It was observed that the values of GOT, GPT and ALP on day 1 and 5 were comparable with the values of the control and treated groups. There were no statistical differences in GOT, GPT and ALP observed between groups, However, Group sacrificed after 1 dayrats showed a significant increase in GOT and elevated but not significant GPT after 1st day and return to normal values after the 5th day.

The histological examination of liver from female' rats were performed in both control and treated groups. All the sampling tissue sections showed no histopathological changes. They were within normal limits. Neither degenerative nor infiltrative lesions were observed.

**Subacute toxicity study of synthetic alkaloids:** A separate experiment was carried out to evaluate the subacute toxicity of synthetic alkaloids (5.2 mg $kg^{-1}$ sulphate atropine and 2.6 mg $kg^{-1}$ bromide scopolamine) in the Wistar rats. The administration of saline water or synthetic alkaloids to four weeks did not induce any marked changes in the general behaviour or physiological activities of the rats however the diarrhoea was observed (Fig. 5).

The treatment of rats with saline or dose synthetic alkaloids (sulphate atropine and bromide scopolamine), did not induce mortality during the whole study period.

The administration of dose synthetic alkaloids resulted in a no significant reduction in the final body weight of the animals when compared with the control (Fig. 6).

The saline and synthetic alkaloids did not cause any gross morphological abnormality in various organs of the animals.

The relative weight of organs showed no significant difference, in comparison with the control group (Table 4).

Table 4: Effect of subacute administration of synthetic tropan alkaloids (atropine and scopolamine) on some haematological parameters in female rats

| Group | RBC ($10^6$ mm$^{-3}$) | MCV | RDW | HCT (%) | PLT ($10^3$ mm$^{-3}$) | MPV | WBC ($10^3$ mm$^{-3}$) | HGB (g L$^{-1}$) |
|---|---|---|---|---|---|---|---|---|
| Control | 7.89±0.49 | 53.97±2.04 | 13.27±1.27 | 42.40±1.77 | 473.66±80.70 | 6.50±0.26 | 14.33±1.60 | 14.56±0.66 |
| Treated for 4 weeks | 7.49±0.56 | 53.05±11.01 | 12.49±0.88 | 41.56±2.70 | 475.27±51.97 | 6.61±0.21 | 10.66±1.81* | 14.30±0.67 |

Values are mean± S.D,*p<0.05, RBC: Red blood cell, MCV: Mean corpuscular volume, RDW: Red cell distribution width, HCT: Hematocrit, PLT: Platelets, MPV: Mean platelet volume, WBC: White blood cell and HGB: Hemoglobin

Table 5: Effect of subacute administration of synthetic alkaloids (atropine and scopolamine) on relative organ weights of female rats

| Group | Liver | Brain | Kidney | Lungs | Heart | Spleen |
|---|---|---|---|---|---|---|
| Control | 0.042±0.0046 | 0.0083±0.00038 | 0.0070±0.00087 | 0.0075±0.00075 | 0.0033±0.00038 | 0.0048±0.00057 |
| Treated for 4 weeks | 0.041±0.0031 | 0.0079±0.00068 | 0.0066±0.00056 | 0.0071±0.00064 | 0.0035±0.00036 | 0.0040±0.00035 |

Values are Mean±SD

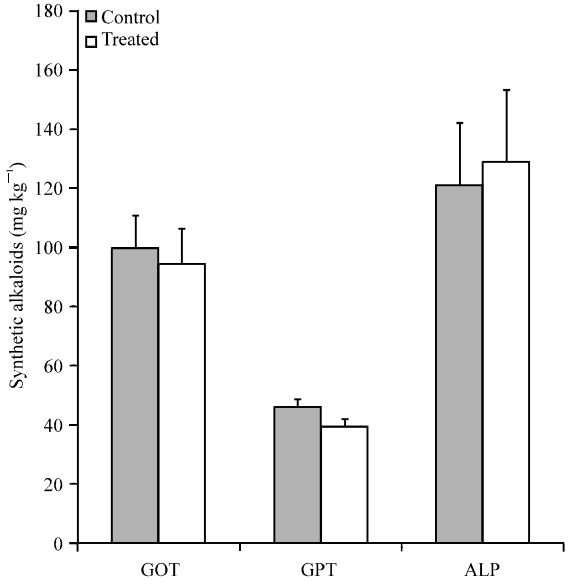


Fig. 6: Effect of subchronic administration of synthetic alkaloids on some biochemical parameters in female. Values are Mean±SD, vertical line on each bar indicates the standard error

**Biochemical and haematological observation:** The haematological values of treated rats were not significantly different from those of control group (Table 5). However, WBC values of the control group were significantly higher than those of the treated group.

The estimation of various enzymes of subacute toxicity revealed no significant differences. Values of serum enzymes GPT, GOT and ALP-treated rats were not changed significantly compared to control rats (Fig. 6).

Under the microscopic examination, the liver of treated-group of subacute toxicity study showed normal conservative cellular and lobular architecture.

## DISCUSSION

*D. stramonium* (called Jimson weed) has been reported as a drug of abuse (Aroukou *et al*., 2003; Chan, 2002; Birmes *et al*., 2002). *Datura stramonium* is known to contain highly toxic tropane alkaloids, including the pharmacologically active compounds atropine and scopolamine (Dugan *et al*., 1989; Desachy *et al*., 1997). But it was reported that this plant is also used in traditional medicine (Pretorius and Marx, 2006; Gidado *et al*., 2007).

HPLC enabled to evaluate the content of the two mains alkaloids. The atropine concentration is higher than that of scopolamine. The separation and values of scopolamine and atropine were in agreement with the ranges previously reported in avaible literature (Friedman, 2004; Miraldi *et al*., 2001).

The toxic effects of a test substance can be basically determined by physical examination, daily observation, visual examination, measure of food and water consumption, body and organ weight, haematology, urinalysis, biochemical organ function tests and pathology studies (Stevens and Gallo, 1989; Maruo *et al*., 2003).

The liver, known to be key organ in the metabolism and detoxification of xenobiotics, is vulnerable to damage induced by a huge variety of chemicals (Udem *et al*., 2010).

An obvious sign of hepatic injury is leakage of cellular enzyme into plasma. When the liver cell membrane is damaged, a variety of enzymes normally located in the cytosol are released into blood stream. The estimation of the GPT and GOT in the serum is a useful quantitative marker for the extent and type of hepatocellular damage (Udem *et al*., 2010; Kumar *et al*., 2004). An increase in the level ALP is an indication of biliary obstruction (Udem *et al*., 2010).

The group treated with 100 mg kg$^{-1}$ total alkaloids did not show a change in the levels of theses enzymes. However, female rats showed a significant increase in GOT and elevated but not significant GPT after 1st day and returned to normal values after the 5th day. This could be explained by rapid metabolism and excretion of alkaloids and their metabolites (Hardman *et al*., 1998). Microscopic examinations of treated-groups show no histopathological changes. This is consistent with the results found by Bouzidi *et al*. (2011), in male ratstreatedin the same conditions.

In the subchronic toxicity study in females rats given the alkaloids intraperitonealy at doses. Since, the changes in body weight have seen used as an indicator of adverse effects of drugs and chemicals (El Hilaly *et al*., 2004), there was no change, weight gains were not significantly different in the treated rats as compared to the controls. This observation of body weight is in agreement to the earlier reports of Gidado *et al*. (2007) and Bouzidi *et al*. (2011) who have noted no change in body weight of seeds *D. stramonium* treated male rats. There is no significant change in other relative organ weight.

GOT and GPT are elevated following tissue damage in which cellular enzymes are released from cells into the bloodstream. GOT is found in high constitutive levels in the heart and liver whereas GPT is most active in the liver. Serum ALP is found in most tissues, including bone, liver and kidney. Elevations are seen following eating and osteoblastic activity, impairment of liver function and obstruction of bile flow, depressions are seen in malnutrition (Udem *et al*., 2010; Maruo *et al*., 2003). There is no alterations in serum constituents in the treated animals. The female group treated with synthetic alkaloids (atropine and scopolamine) did not show change in the level of enzymes ALP, GOT and GPT after one monthof treatment with syntheticalkaloids. This is in agreement with the works of Gidado *et al*. (2007) where they have treated rats with alcoholic extract of leaves of *D. stramonium* for five weeks.

The resultants of the present study show no alterations in haematological parameters after 4 weeks of alkaloids exposure. This observation on this observation on liver enzymes and haematological parameters is not consistent with studies by Bouzidi *et al*. (2011) Which in the male rats are treated in the same conditions.

## CONCLUSION

Although, it seems that female rat smetabolize quickly alkaloids of Datura, the study did not establish the complete safety of the alkaloids of *D. stramonium* as the administration of total alkaloids of the seeds of *D. stramonium* and alkaloids synthetic for four weeks for rats are likely to be toxic too their organs like the brain at higher doses and a prolonged time.

## ACKNOWLEDGMENTS

We would like to think ANDRS, Oran Algeria, for financial support of the project. We also thank Prof Touabti Director of Central Laboratory and the staff of the laboratory of anatamo-pathology of the Hospital of Setif Algeria and Pr JP Angers de Rennes.

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