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# CHEMICAL COMPOSITION OF ESSENTIAL OIL AND EVALUATION OF ACUTE AND SUB-ACUTE TOXICITY OF *DOREMA AMMONIACUM* D. DON. OLEO-GUM-RESIN IN RATS

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## Abstract

**Background:** *Dorema Ammoniacum* is a perennial herb which has been used in Persian Traditional Medicine for different indications, including gastrointestinal disorders and sciatica. Despite numerous medicinal uses, there is a lack of toxicological studies on *Dorema Ammoniacum*; therefore, the aim of the present study is to investigate its possible toxic effects as well as the determining chemical composition of its essential oil.
**Materials and Methods:** Acute toxicity study was performed by administration of single increasing geometric doses of oleo-gum-resin solution (1250, 2500, and 5000 mg/kg) to Wistar rats. For sub-acute toxicity study, repeated doses of oleo-gum-resin solution (100, 200 and 500 mg/kg) were administered orally to rats for 4 weeks. At the end of the treatment, histopathological studies, hematological assessments, and biochemical parameters were performed.
**Results:** GC-MS was performed to determine the chemical composition of the essential oil. Acute toxicity results demonstrated no mortality, and the Median Lethal Dose (LD50) was greater than 5000 mg/kg. Sub-acute treatment did not show any significant changes in biochemical and hematological parameters at any doses compared to the control group. Histopathological analysis of the organs revealed varying effects. At the level of the liver, vacuolar degeneration and mild inflammation at 200 and 500 mg/kg doses were observed. At the level of kidney, congestion of glomeruli and a widening of the urinary space at 500mg/kg were observed compared to the control group. The principle components of the essential oil were Cuperene (14.31%) and β-Funebrene (12.74%).
**Conclusion:** The results suggest that the acute administration of the oleo-gum-resin of *D. Ammoniacum* is not accompanied with signs of toxicity; however, its administration over the long term might associate with renal toxicity and hepatotoxicity.

**Keywords:** gum ammoniac, toxicity, hematology, histopathology, biochemistry

## Introduction

The genus *Dorema* from Apiaceae family includes 12 species that are mainly distributed in central and southwest Asia. In Iran, this genus is represented by seven species, one of which is *Dorema Ammoniacum* D. Don. (Flora of the U.S.S.R, 1974). *D. Ammoniacum* is a monocarpic perennial plant which grows up to 2.5m high in Iran, Afghanistan, Pakistan, and North India. In Iran, it is known by the local Persian names of "Oshagh", "Vasha", "Kandal", "Koma-Kandal" (Mozaffarian, 2008). Its naturally-exuding oleo-gum-resin latex, commonly known as gum ammoniacum, is found in cavities, stems, roots, and petioles. It serves as an antispasmodic, expectorant, carminative, diaphoretic, mild diuretic, poultice, stimulant, antimicrobial, spleen and liver tonic, anticancer, and vasodilator (V M Flora of Iran, Eskandani et al., 2014, Javadi et al., 2015, Naghibi et al., 2015, Sharafzadeh et al., 2012). Recently, a low cytotoxic activity was detected for the essential oil of *D. Ammoniacum* fruit. Several studies have proved significant antimicrobial activity of the fruit essential

oil and oleo-gum-resin from *D. ammoniacum* (Rajani et al., 2002, Shahidi et al., 2002, Yousefzadi et al., 2011). Abizadeh et al. reported that oleo-gum-resin has anticonvulsant effect on PTZ- induced model of epilepsy (Abizadeh et al., 2014).
Since there is a lack of toxicological studies despite the various pharmacological activities, this study is designed to evaluate acute and sub-acute toxicity of *D. Ammoniacum* oleo-gum-resin. Moreover, due to the lack of studies on the chemical constituents of gum ammoniac, the chemical composition of the essential oil of the mentioned oleo-gum-resin has also been investigated.

## Materials and Methods

### Test Substance

The oleo-gum-resin (DAOGR) was purchased from the market, and was authenticated by the botanist as *Dorema Ammoniacum* D. Don. (voucher number: PMP-823). Afterwards, DAOGR was grounded, sieved from mesh 30, and dissolved in distilled water for oral administration.

### The Composition the Essential Oil of DAOGR

The essential oil of oleo-gum-resin was obtained by steam-distillation method using Clevenger apparatus. The essential oil was analyzed by using an Agilent 7890 gas chromatography (GC) system equipped with a HP5 column (30 m× 0.25mm, film thickness 0.25 µm). The column temperature was programmed from 60°C to 250°C, and being held for 5 minutes at a rate of 3°C/min; it also was programmed to 300°C, and being held for 3 minutes at a rate of 10°C/min. The injector temperature was set at 290°C. Helium was used as a carrier gas with a flow rate of 0.8 mL/min. Mass spectroscopy was Agilent 5973 model mass detector with electron ionization (EI) system with ionization energy of 70 eV, and the ionization source temperature was set to 220°C. For GC and GC-MS analysis, 1µL of the essential oil dissolved in hexane was injected by the split mode (1:25). Electronic integration of the FID peak areas was used for determination of the quantitative data. MSD Chemstation software (Aglient Technologies) was used for data analysis. Components were identified by using their retention times to n -alkanes compared to those of Wiley 275 library and those described by Adams (Farzaei et al., 2014; Adams, 2004).

### Animals

Eighty healthy, 8-week-old Wistar albino rats consisting of 40 males (230 ± 5 g) and 40 females (210 ± 5 g) were selected from the animal lab of the Faculty of Pharmacy at Tehran University of Medical Sciences, Tehran, Iran.
The animals were housed in a room temperature (22 ± 2°C), a relative humidity of 50±20%, and 12h/12h light/darkness, and were fed with commercial standard rat chow and water ad libitum. All the ethical guidelines for use of laboratory animals were followed carefully , and the study was ethically approved by TUMS (Tehran University of Medical Sciences) Review Board. Following several days of acclimatization, rats were randomly assigned to control and experimental groups.

### Acute oral toxicity

Forty rats were randomly divided into four groups, each of which consisting of ten animals (n=5 male and n=5 females): a control (Group 1) and three dose level groups (Group 2, 3, and 4) received a single dose of 1250, 2500 and 5000 mg/kg body weight, respectively. DAOGR was administered once by oral gavage at 10ml/kg body weight while distilled water was administered to control group. After administration, the animals were first observed every half hour for 4 hour, and daily thereafter. Changes in eyes, skin and fur, and mucus membrane (nasal), as well as the behavioral changes such as salivation, diarrhea, and body weight were observed and recorded separately for each animal in comparison to the controls during the experiment. On day 14, after administration, the animals were sacrificed by chloroform inhalation, and their external surface, thoracic organs, and abdominal organs and contents were macroscopically examined (kebede et al., 2016, Lee et al., 2015).

### Four-week Repeated-dose Oral Toxicity (Sub-acute Toxicity)

The remaining rats were randomly distributed into four groups (n=5 males and 5 females/ group): a control (Group 1) and three dose level groups (Groups 2, 3, and 4) were administered 100, 200, and 500mg/kg body weight/day, respectively. DAOGR was administered by oral gavage at 10ml/kg body weight on a daily basis for 4 weeks. The control animals were treated with the same volume of distilled water.

### *In vivo* Observation

During the experiment, the animals were observed for signs of toxicity and mortality twice a day. Detailed toxicological signs were assessed and recorded, including changes in skin and fur, eyes, mucous membranes, manure, behavioral patterns, etc. (Lee et al., 2015, Xie et al., 2013).

### Ophthalmoscopy

Eye examination was performed shortly before the start of the experiment and prior to its termination according to the methods prescribed by Lee et al., 2015 (Lee et al., 2015).

**Body Weight:** The body weight was measured at the onset and once a week during the experiment.

### Food Intake

The amounts of food were weighed before being supplied to each cage, and their remnants were also measured the next day. The differences were reported as daily feed consumption.

### Hematology and Serum Biochemistry

Hematological and biochemical parameters have been assessed according to methods described previously (Lee et al., 2015, Xie et al., 2013).

### Organ Weights

At the end of the treatment period, all male and female rats were anesthetized by chloroform. The anesthetized animals were sacrificed, and then decapitated for blood collection. Complete gross postmortem examination was performed on all animals. All organs were carefully examined macroscopically. Afterwards, the liver, lungs, heart, kidneys, spleen, and stomach were separated and after fat removal, all of their connective tissues and blood were weighed (Lee et al., 2015, Xie et al., 2013).

### Histopathology

Hematoxylin and eosin staining was used for microscopic examination of organs, including brain, thyroid glands, stomach, small intestine, large intestine, pancreas, lungs, spleen, kidneys, liver, heart, bladder, testes, ovaries, uterus, and prostate gland (Lee et al., 2015, Xie et al., 2013).

### Statistical Analysis

The data are expressed as the means ± SEM. The data were analyzed by the one-way analysis of variance (ANOVA) followed by Fisher's Least significant difference test using SPSS program. Data from male and female animals were analyzed separately. A $P<0.05$ was considered significant.

## Results

### The Essential Oil Yield and Composition

The yield of essential oil extraction was 0.6% seperately. Forty-two constituents were identified that represented 60.05% of the total oil. The chemical composition of the essential oil is demonstrated in table 1. The principle components of the essential oil were Cuperene (14.31%) and β-Funebrene (12.74%).

| **Table 1:** The essential oil composition of *Dorema Ammoniacum* of oleo-gum-resin | | | |
|---|---|---|---|
| | Retention Time | Area% A1 | Compound |
| 1 | 17.87 | 14.31 | Cuparene |
| 2 | 15,65 | 12.74 | β-Funebrene |
| 3 | 16,38 | 9.21 | Barbatene |
| 4 | 17,27 | 7.46 | Germacrene D |
| 5 | 10,98 | 6.68 | Z-Ocimenone |
| 6 | 17.92 | 4.91 | Bisabolene |
| 7 | 16,58 | 4.25 | α-Humulene |
| 8 | 16,67 | 3.85 | Amorpha-4,11-diene |
| 9 | 11.17 | 3.31 | E-Ocimenone |
| 10 | 8.34 | 3.23 | 2,6-Dimethyl3,5,7-octatriene-2-ol,,Z,Z |
| 11 | 17.18 | 3.13 | β-Chamigrene |
| 12 | 4.2 | 2.89 | α-Pinene |
| 13 | 16.33 | 2.5 | Guaiadiene |
| 14 | 11.02 | 2.43 | Thymol methylether |
| 15 | 15.03 | 2.38 | β-elemene |
| 16 | 15.74 | 2.13 | Trans-caryophyllene |
| 17 | 17.71 | 1.83 | Himachalene |
| 18 | 18.24 | 1.68 | δ-Cadinene |
| 19 | 10.36 | 1.49 | 2,6-Dimethyl3,5,7-octatriene-2-ol,,E,E |
| 20 | 14.62 | 1.36 | α-Copaene |
| 21 | 16.45 | 1.31 | β-Selinene |
| 22 | 17.59 | 1.27 | α-Selinene |
| 23 | 16.73 | 0.56 | Acoradiene |
| 24 | 15.79 | 0.56 | Cedrene |
| 25 | 18.47 | 0.55 | γ-Cuprenene |
| 26 | 16.19 | 0.54 | Elemene |
| 27 | 4.96 | 0.45 | β-pinene |
| 28 | 18.39 | 0.44 | Dauca-4(11),8-diene |
| 29 | 19.04 | 0.35 | Dauca-4(11),8-diene |
| 30 | 14.85 | 0.34 | β-burbonene |
| 31 | 16.88 | 0.33 | Aromadendrene |
| 32 | 21.8 | 0.28 | Bulnesol |
| 33 | 17.38 | 0.27 | β-selinene |
| 34 | 16.03 | 0.27 | Thujopsene |
| 35 | 8.1 | 0.24 | 2,6-Dimethyl1,3(E)-5(Z),octatetraene |
| 36 | 19.9 | 0.14 | Caryophyllene oxide |
| 37 | 9.26 | 0.13 | Dimercaprol |
| 38 | 10.12 | 0.07 | Myrtenol |
| 39 | 13,92 | 0.05 | α-cubebene |
| 40 | 5.88 | 0.04 | p-cymene |
| 41 | 5.96 | 0.02 | Limonene |
| 42 | 4.06 | 0.01 | α-thujene |
| Total identified: 60.05 | | | |

**Acute Oral Toxicity Evaluation**

No animal death was recorded during the experiment. The animals did not manifest any significant DAOGR-related effects evident concerning the toxicological signs, body weight changes, and macroscopic findings at any time of observations and at any administered doses. Autopsy results showed no remarkable changes or lesions in any animal.

**Repeated Dose 28-Day Oral Toxicity (Sub-acute Toxicity)**
**General Appearance, Body Weight, Food Intake, and Water Consumption**

In sub-acute toxicity study, no death or remarkable changes of toxicological signs associated with the administration of DAOGR were observed during the experiment at any administered doses. In addition, there were no statistically significant changes in body weight in the DAOGR-treated groups compared to the control group. No statistically significant differences in food consumption of male rats were recorded between the control and treatment group; however, a statistically significant increase in food consumption was observed in the 200mg/kg-administered female groups on week 2 and 4 compared to control group ($P<0.05$).

**Hematological and Biochemical Findings**

There were no significant changes in the hematological or biochemical parameters in rats after 28 days of DAOGR treatment (Table 2).

**Table 2:** Hematological and biochemical parameters of sub-acute oral administration of DAOGR (4 weeks)

| | Sex | Dose 0 | Dose 100 | Dose 200 | Dose 500 |
|---|---|---|---|---|---|
| RBC (M/µL) | Male | 9.2±1.17 | 9.2±2.27 | 8.4±2.33 | 8.9±2.29 |
| | Female | 9.3±0.98 | 9.1±2.13 | 9.2±2.31 | 9.1±2.2 |
| Hb (g/dl) | Male | 16.7±2.1 | 16.9±1.4 | 14.9±4.5 | 15.7±4.3 |
| | Female | 16.3±1.1 | 15.9±0.87 | 15.9±3.5 | 15.7±4.3 |
| HCT (%) | Male | 46.5±4.6 | 48.5±3.9 | 41.9±12.7 | 43.3±12.2 |
| | Female | 45.5±3.1 | 46.5±4.2 | 46.7±5.1 | 44±6.3 |
| MCV (fl) | Male | 50.6±1.8 | 52.8±2.9 | 50.2±14.3 | 48.8±13.6 |
| | Female | 51.1±2.5 | 48.8±3.2 | 49.1±3.6 | 52.3±5.6 |
| MCH (pg) | Male | 18.1±0.28 | 18.3±0.58 | 17.8±5.1 | 17.6±4.9 |
| | Female | 18.2±0.67 | 18.1±0.29 | 18.8±4.3 | 17.6±3.3 |
| Platelet count (1000/µL) | Male | 448.6±78.5 | 613.7±70.4 | 501.8±158.5 | 481.2±152.6 |
| | Female | 538.5±45.1 | 593.3±56.1 | 532.5±134 | 498.5±96 |
| WBC (1000/µL) | Male | 8.3±1.6 | 7.5±2.1 | 7.8±2.7 | 9.4±3.04 |
| | Female | 8.1±0.4 | 7.5±2.1 | 6.8±3.1 | 7.4±3.2 |
| LYM (%) | Male | 79.3±3.01 | 71.8±9.1 | 67.7±20.6 | 69.03±9.9 |
| | Female | 69.3±7.1 | 71.6±8.5 | 68.7±10.1 | 69.4±5.8 |
| MON (%%) | Male | 5.27±3.01 | 6.8±2.06 | 6.48±2.4 | 5.02±2.4 |
| | Female | 6.88±1.4 | 6.02±3.45 | 6.48±1.1 | 6.02±3.7 |
| PT (s) | Male | 11.5±0.9 | 12.1±0.7 | 12.1±0.4 | 11.9±0.3 |
| | Female | 10.1±0.8 | 9.1±0.4 | 9.2±0.3 | 8.9±0.4 |
| Blood Sugar (mg/dl) | Male | 156.3±13.5 | 167.3±46.3 | 170.3±46.2 | 144.1±45.5 |
| | Female | 160.1±11.2 | 170.4±21.3 | 170.4±11.3 | 156.2±46.2 |
| Blood Urea Nitrogen(mg/dl) | Male | 50.66±2.6 | 63.2±16.1 | 54.7±15.2 | 55.7±14.9 |
| | Female | 54.7±16.1 | 56.2±3.1 | 61.3±15.1 | 55.7±14.5 |
| Cholesterol (mg/dl) | Male | 65±4.3 | 81.6±20 | 59.7±19.5 | 56.5±18.9 |
| | Female | 67±11.1 | 69.2±6.6 | 58.3±14 | 58.2±11.5 |
| Triglycerides (mg/dl) | Male | 156±47.9 | 143.4±41.6 | 147.1±39.8 | 146±38.9 |
| | Female | 147.4±19.1 | 146±50.2 | 147.1±36 | 156±28.4 |
| AST (U/L) | Male | 131±18.5 | 114.5±32.4 | 118.2±32.4 | 129.5±33.6 |
| | Female | 124±26.1 | 128.2±22.4 | 119.5±22.1 | 118.1±41.1 |
| ALT (U/L) | Male | 44±5.4 | 33.8±6.7 | 41.8±9.9 | 46.7±11.5 |
| | Female | 43±2.4 | 43.8±3.5 | 41.8±6.9 | 44.7±2.4 |
| ALP (U/L) | Male | 350.3±88.8 | 312.3±96.8 | 457.2±133.7 | 391.6±135.3 |
| | Female | 368±56.1 | 380.6±76 | 417.1±78.4 | 407.2±102.5 |
| Total Protein (g/dl) | Male | 6.7±0.3 | 7.7±1.8 | 6.3±1.8 | 6.5±1.8 |
| | Female | 7.1±1.3 | 6.3±0.8 | 6.5±1.2 | 7.1±0.3 |
| LDH(U/L) | Male | 1292.5±305.8 | 998.3±347.7 | 1046.8±356.2 | 1029±382.9 |
| | Female | 999.8±361.7 | 1045.8±344.5 | 1019±412.9 | 1020.8±350.2 |
| CREA (mg/dl) | Male | 0.63±0.04 | 0.7±0.17 | 0.63±0.17 | 0.62±0.17 |
| | Female | 0.58±0.09 | 0.63±0.07 | 0.58±0.07 | 0.61±0.16 |

**Organ Weight**

The organ weight changes were not considered to be associated with the toxicological changes between the control group and DAOGR-treated group at the end of the experiment for either gender.

**Histopathology Findings**

Histopathology analysis of organs' portions after treatment with DAOGR revealed varying effects. The major pathological findings included some toxicity signs in the liver and the kidneys. At the level of the liver, vacuolar degenerescence and mild inflammation at 200 and 500 mg/kg doses were observed. At the level of the kidneys, congestion of glomeruli and a widening of the urinary space at 500mg/kg dose in comparison to the control group were observed (Figure 1).

## Discussion and Conclusion

Despite a wide variety of preclinical and clinical studies to evaluate efficacy of medicinal herbs, the number of investigations addressing their safety and toxicity are few (Xie et al., 2013). Because of the extensive use of DAOGR in Persian Traditional Medicine, this study intends to evaluate its safety through oral acute and sub-acute (repeated Dose 28-Day) toxicity tests. Before safety evaluation, the chemical composition of DAOGR's essential oil was identified by GC-MS. As mentioned eralier, the principle components of essential oil were cuparene (14.31%) and β-Funebrene (12.74%). There are several published papers which describe the structure of some other chemical compounds from *Dorema Ammoniacum*. A spiro-chromene derivative, doremone A, dashamirone, and ammoresinol were identified as major compounds in dichloromethane extract of gum resin via HPLC assay analysis (Adhami et al., 2013). The chemical composition of the essential oil from *Dorema Ammoniacum* oleo-gum-resin has been investigated in this study for the first time. The chemical composition of the essential oil from *Dorema Glabrum* revealed delta-Cadinene (12.77%) as the main component of the root that is followed by beta-bisabolene (7.48%), alpha-Fenchyl acetate (6.32%), and Copaene (5.68%) (Asnaashari et al., 2011); while elemicin (38.6%) and myristicin (14.3%) were reported as main compounds of aerial parts (Delnavazi et al., 2015). The investigation of *Dorema Aucheri*'s essential oil revealed β-caryophyllene, thymol, β-gurjunene, carvacrol, and cuparene as the major components (Akbarian et al., 2016).
The acute toxicity study showed no DAOGR-related mortality or adverse effects at any doses by oral administration during 14 days. Also, normal body weight gains were observed in the males and females of all dose groups, and the changes in body weight were not significant at any doses.

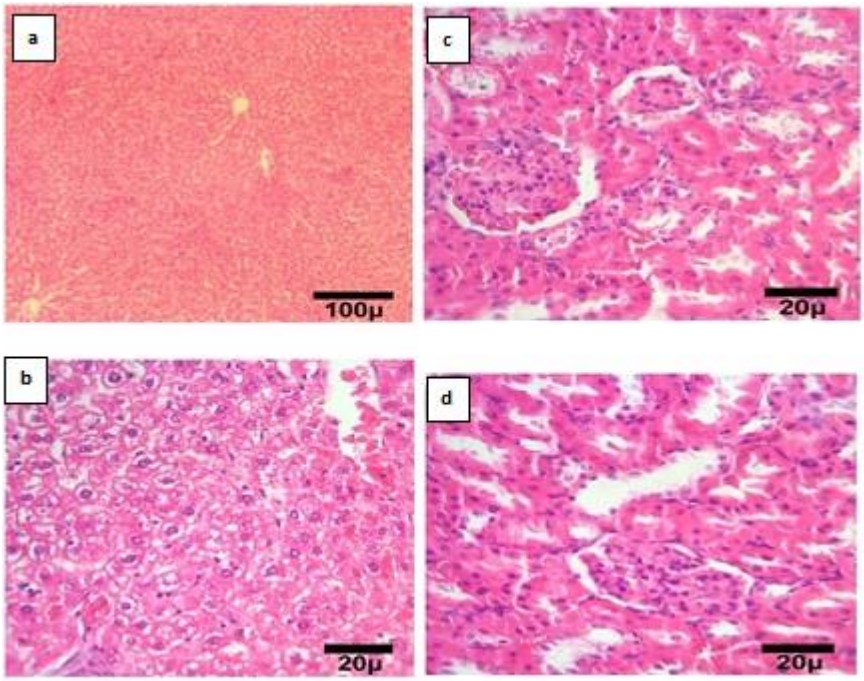


**Figure 1**: Histology of organs of rats exposed to DAOGR for 28 days. a) Liver: vacuolar degenerescence × 100; b) Liver: vacuolar degenerescence × 400; c) kidney: congestion of glomeruli; d) kidney: widening of the urinary space

The results suggested that acute administration of the oleo-gum-resin of *D. Ammoniacum* is not associated with signs of toxicity, and it leads to estimation of Median Lethal Dose (LD50) DAOGR higher than 5000 mg/kg in rats.
Daily oral administration of DAOGR for 28 days had no effect on body weight, food and water consumption, absolute and relative organ weight, as well as the hematology test. However, histopathological examination of animal groups receiving the oleo-gum-resin for 28 days demonstrated some signs of hepatotoxicity and kidney toxicity. Vacuolar degenerescence in the liver section could be due to the inflammation or blockage role of the DAOGR on the walls of blood vessels. The congestion of glomeruli and widening of the urinary tract may be due to the effect of DAOGR on capillary constriction to decrease glomeruli filtration. Mostafavi et al. showed that intraperitoneal injection of *Dorema Aucheri* leaves extract caused necrosis, inflammation of the liver tissue, cell proliferation, cholestasis, and significant increase in release of liver enzymes (ALP, SGPT and SGOT) and bilirubin in mice (Mostafavi et al., 2013). However, Ahangarpour et al. demonstrated hepatoprotective effects of *Dorema Aucheri* leaves hydroalcoholic extract in nicotinamide-streptozotocin induced type 2 diabetic rats at dose of 200 mg/kg for 4 weeks by reversing back the elevated level of liver enzymes (SGOT and SGPT) (Ahangarpour et al., 2014).
In conclusion, it seems that DAOGR is safe in acute administration, however, long term use might be associated with sign of hepatotoxicity and kidney toxicity. Sub-chronic studies are recommended to confirm obtained results.

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**Conflict of Interest:** The authors declare that they have no conflict of interest.

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