Acute and Sub-acute Oral Toxicity Studies of Majoon-IQ – A Unani Brain Tonic

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Abstract

Majoon-e-IQ is a Unani herbal formulation and used as a brain tonic. The objective of this study was to investigate the acute and sub-acute oral toxicity of Majoon-IQ in Wistar Albino rats of either sex. Acute oral toxicity study was conducted as per OECD-425 guideline in which Majoon-IQ was administered at a dose level of 5000mg/kg b.w. to both male and female rats and the animals were then observed individually for 30 minutes, 4 hour post dosing and at least twice daily for 14 days. Sub-acute oral toxicity study was conducted as per OECD-407 guidelines. In sub-acute oral toxicity study Majoon-IQ was administered at the dose level of 4800 mg/kg b.w. in a single bolus everyday for 28 days. The rats were observed daily during the period of study. After overnight fasting, rats were sacrificed on 15th day and 29th day. Observation parameters included a comparative evaluation of the general appearance/behaviour, morbidity/mortality, body weights, food/water consumption, haematology parameters, bio-chemistry parameters and histopathology of major organs of treated and control groups. No any adverse effect was observed in both the toxicity studies indicating that Majoon-IQ is free from any toxic effects under the conditions of these studies.

Keywords: Majoon-IQ; Brain tonic; OECD guidelines; Acute toxicity; Sub-acute toxicity.

Introduction

Unani system of Medicine originated from Greece. Hippocrates (460-377 BC) was the ancient Greek philosopher-physician who freed Medicine from the sphere of magic and superstition (Ahmad *et al.* 2010). The fundamentals of Unani medicine are based on his teachings. After Hippocrates, a number of other Greek scholars enriched the system significantly. Among them, Galen (131-210 AD) was the one who strengthened its foundation on which Arab physicians like Rhazes (850-1037 AD) and Avicenna constructed a huge and magnificent structure (Anonymous 2007; Chaudhary *et al.*, 2013). The Unani system of medicine in which plants (whole or parts) are used as herbal drugs to cure various ailments. Its use is quite prevalent and has potential for improving health and lowering the cost of treatment and thus makes health care affordable by all. A lot of herbs are used still for treating various diseases; the reason behind this is that most of the people believe that they have less toxic effects and more synergic effects (Azmat *et al.*, 2012). The literature on herbal medicine mentions several herbs exerting influence on brain function in general and memory in particular (Steven *et al.*,2002) Various Unani preparations are being used as a brain tonic. One such preparation is Majoon-IQ which is used as a brain tonic. Efficacy of Majoon-e-IQ is well defined but limited data are available pertaining to its toxicity profile as per the standard guidelines.

In this study, an effort was made to generate the toxicity profile of Majoon-IQ as per internationally accepted standards. Dosage of Majoon-IQ in Humans is 16

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grams per day. Majoon-IQ was administered to human subjects every day which amounts to 230mg/kg/day dose. The dosage in acute study was 5000mg /kg body weight which is the limit of dose while as the dosage for sub-acute study was 4800mg/kg body weight as it corresponds to the 3X of the rate extrapolated dose, while as X is the extrapolated dose. In order to assess the potential toxic effects of Majoon-IQ, it was administered to young, healthy rats at different dose levels in the two different acute and sub-acute safety studies.

Table 1: Constituents of Majoon-IQ

S. No.	Ingredients	Botanical/ English Name	Part Used	Quantity
1.	Brahmi	*Bacopa monnieri* L.	Whole plant	40 g
2.	Asgandh	*Withania somnifera* L.	Root	40 g
3.	Filfil Safaid	*Piper nigrum* L.	Fruit	40 g
4.	Badam	*Prunus amygdalus*	Seed	80 g
5.	Khajoor	*Phoenix dactylifera* L.	Fruit	80 g
6.	Asal	Honey	---	1.2 kg

Material and Methods

Test Item.

The work was carried on Majoon-IQ supplied by CRIUM, Hyderabad and the date of manufacture was August 2014. Majoon-IQ was available as a semisolid paste which was mixed with distilled water to make the suspension.

Animals and Exposure Conditions

The experimental animals (young, healthy Albino rats of Wistar Strain of either sex) were procured from Indian Institute of Integrative Medicine, Jammu. These rats were kept in the animal house as per the International standards (Animal Research Review Panel, 2002) and observed during the quarantine and acclimatization period (Capdevila *et al.*, 2007). A veterinary examination was done on the rats prior to and at the end of the acclimatization and quarantine period of 14 days. The rats were housed under standard environmental condition i.e. temperature of 22 ± 2^{o}C with 12:12 hour dark and light cycle. The rats were provided pelleted feed procured from Pranov Agro Industries, New Delhi and distilled water ad libitum. The experimental work was carried out as per the guidelines set by CPCSEA, India. The study was approved by the IAEC, Regional Research Institute of Unani Medicine, Srinagar which is registered with CPCSEA, India with registration No. 927/GO/C/06/CPCSEA.

Acute Oral Toxicity Study

The acute oral toxicity test was carried as per (OECD 425, 2008). Albino rats of either sex 100-150 grams body weight (8-12 weeks of age) were used. Five animals of each sex were used in each of the two treated and control groups (total 20 animals). All the rats were weighed to record their initial body weight at

intial stage and on the 8th and 15th day of the experiment. The test substance was administered orally by using feeding canula. Rats were fasted overnight but allowed water ad libitum prior to feeding of drug. The Group I and II were the male and female Controls and given RO water in comparable volumes to the treated animals in a single bolus (Vehicle only). Animals of Group III (males) and IV (females) were treated with the Majoon-IQ at the dose level of 5000 mg per kg body weight suspended in distilled water. All the rats were observed individually for any acute toxicity signs and behavioural changes at an interval of 30 minutes, 4 hour post dosing and once daily for 14 days. During the study period of 14 days, the feed and water consumption / animal / 24 hours were recorded at the initial stage, after 1 week of dosing and at the end of the study. On the 15th day all the animals were sacrificed by exsanguinations by withdrawing blood in a syringe from the dorsal vena cava after opening the abdomen under ISOFLURANE anaesthesia. Two millilitre of blood was added to EDTA vacutainer for the study of Haematological parameters and 3 ml blood was added to Red tap vacutainer containing the clotting activators. The clotted blood was centrifuged and the serum was separated for the study of bio-chemistry parameters. The internal organs were examined macroscopically for the visualization of morphological changes, if any.

Sub-Acute Oral Toxicity Study

The Sub-acute Oral Toxicity was conducted in accordance with the OECD-407 Guideline. The rats were randomly divided into 4 groups and each group consisted of 5 rats. The Groups I and II were the male and female Controls and orally treated with distilled water (Vehicle) and Groups III and IV were the male and female experimental and orally treated with Majoon-IQ single dose of 4800mg/kg body weight for 28 days daily. All the animals were closely observed for the first 1 and 4 hours of dosing to examine any adverse toxic signs, behavioural changes etc. The body weight of the rats was evaluated weekly. Food and Water consumption / animal / 24 hours were recorded before dosing and then weekly up to 4 weeks. On the 29th day, after over-night fast, all the animals were sacrificed by exsanguinations by withdrawing blood in a syringe from the dorsal vena cava after opening the abdomen under ISOFLURANE anaesthesia. Two millilitre of blood was added to EDTA vacutainer for the study of Haematological parameters and 3 ml blood was added to Red tap vacutainer containing the clotting activators. The clotted blood was centrifuged and the serum was separated for the study of bio-chemistry parameters. All the animals were dissected to check macroscopic morphology of the body organs. The organs such as liver, lung, kidney, adrenal gland, pancreas, spleen, brain, ovary/testes and heart were collected to determine the relative organ weight followed by grossing for the collection of tissues for Histopathological studies.

Assessment of Haematological Parameters

Haematological parameters were analyzed in freshly collected blood in blue top vacutainer containing EDTA anticoagulant. The blood was gently mixed with the

EDTA anticoagulant coated on the tube walls. Haematological parameters were determined on a fully automatic haematological analyzer (Sysmex XT2000iV Sysmex Corporation, Japan). Haematological parameters such as Haemoglobin conc., WBC count, RBC count, haematocrit value, Mean Corpuscular Volume, Mean Corpuscular Haemoglobin Concentration, Mean Corpuscular Haemoglobin, Platelet count, differential leukocyte count – Neutrophil %, Lymphocyte %, Monocyte %, Eosinophil % and basophil %, and Reticulocyte count were studied.

Assessment of Bio-Chemical Parameters

Bio-chemical parameters were studied in serum obtained after centrifugation of blood at 2000 RPM for 15 minutes on the day of the rat sacrifice. Bio-chemical parameters were determined on a fully automatic bio-chemistry analyzer (XL640 TRANSASIA) using ERBA kits. Liver function tests- aspartate aminotransferase AST, alanine aminotransferase ALT, alkaline phosphotase ALP, Total bilirubin, total protein and albumin, kidney function tests- blood urea, uric acid, creatinine and other bio-chemical substances such as glucose, Cholesterol, Triglycerides and HDLC were estimated.

Histopathology

Tissue samples were collected from the organs of control as well as from treated male/female rats of the Sub-acute study. The tissue collected from the organs such as liver, lung, kidney, adrenal gland, pancreas, spleen, brain, ovary/ testes and heart ware numbered for identification and then transferred to tissue cassettes (SS) to enable fixation in 10 % formalin for 36-48 hours followed by the tissue processing which was carried on Automatic tissue processor Model No1020 (LIECA make, Germany). The tissue processing included dehydration in graded isopropyl alcohol, clearing in xylene I and xylene II, impregnation in paraffin wax and finally tissue blocks was prepared on paraffin block maker Model No1150H+C (LIECA make Germany). Section cutting of tissue blocks was done using microtome (YARCO) to the thickness of 4 – 5 microns.

The tissue sections were fixed on the slide by heat technique followed by staining (Haematoxylin and Eosin stain). The staining was carried on Automatic slide stainer (THERMO MAKE, Germany) haematoxylin and eosin staining. After staining, the tissue section was mounted with DPX to prevent any damage to the stained tissue. The stained tissue sections were examined under microscope 40x and 10x objective to check the adverse effects of drug on cell morphology as well as on the cell organelles.

Statistical Analysis

All the results are expressed as mean ± SD. Comparison of all the results on body weight, food and water consumption, haematological value and bio-chemical values were performed by one way analysis of variance (ANOVA) method using

statistical software Graph Pad Prism version 6.05. Probability of 0.05 or less ($p \leq 0.05$) was used as the criterion of significance.

Results

Acute Oral Toxicity Test

Group Mean Body Weight

The rats treated with Majoon-IQ at the dose of 5000mg/kg of body weight were found to grow and gain body weight normal and no deleterious effect was found on their body weight. Table 2 shows the body weight of rats in acute toxicity study.

Table 2: Body Weight of Rats in Acute Toxicity Study

Group	**Days**		
	Day 0 Mean ± SD	**Day 7 Mean ± SD**	**Day 14 Mean ± SD**
Male Control	140.8 ± 5.5	187.4 ± 14.3	213.4 ± 19.4
Male Treated	128.4 ± 5.8	168 ± 13.9	191 ± 19.4
Female Control	120.4 ± 5.8	154.8 ± 6.0	166.4 ± 9.4
Female Treated	133 ± 18.2	154 ± 11.9	177.6 ± 9.0

*The values are expressed as mean ± SD n=5 in each group. *p<0.05 as compared to control at the same time (one-way ANOVA followed by Dunnett's multiple comparison test).*

Group Mean Food and Water Consumption

No significant change was observed in the feed and water consumption in rats after treatment with Majoon-IQ as compared to the control group rats as shown in Table 3.

Table 3 : Average Feed and Water Consumption by Rats

Group Mean Food Consumption Per Rat/24 Hours. (Grams)				**Group Mean Water Consumption Per Rat/24 Hours.(Millilitre)**	
	Male (Mean±SD)	**Female (Mean±SD)**		**Male (Mean±SD)**	**Female (Mean±SD)**
Control	18.46 ± 1.5	18.22 ± 2.0		27.54 ± 1.1	26.33 ± 2.0
Treated	18.39 ± 1.1	17.24 ± 1.0		26.27 ± 2.2	27.32 ± 0.5

*The values are expressed as mean ± SD n=5 in each group. *p<0.05 as compared to control at the same time (one-way ANOVA followed by Dunnett's multiple comparison test).*

Haematological Parameters

The results of haematological parameters of the treated male and female rats did not show any significant change in the values when compared to the respective controls as indicated in Table 4.

Table 4: Haematological Parameters of Rats in Acute Toxicity Study

Parameter	Male		Female	
	Control (Mean±SD)	Treated (Mean±SD)	Control (Mean±SD)	Treated (Mean±SD)
WBC (10^3/µl)	11.17 ± 3.26	10.16 ± 0.91	11.54 ± 0.41	10.31 ± 1.04
RBC (10^3/µl)	7.63 ± 0.32	8.38 ± 0.26	7.59 ± 0.24	7.49 ± 0.23
Hb (grams %)	15.10 ± 0.45	16.10 ± 0.50	15.46 ± 0.33	14.68 ± 0.47
HCT (%)	44.54 ± 1.87	45.27 ± 1.09	45.48 ± 1.00	42.20 ± 1.54
MCV (Femtolitre)	58.44 ± 1.43	59.97 ± 0.59	60.04 ± 1.93	56.03 ± 0.83
MCH (pico grams)	19.84 ± 0.47	20.40 ± 0.17	20.40 ± 0.44	19.62 ± 0.27
MCHC (grams %)	33.96 ± 0.41	34.00 ± 0.40	34.00 ± 0.51	34.82 ± 0.32
Reticulocytes (%)	3.15 ± 0.08	2.6 ± 0.09	3.17 ± 0.66	3.55 ± 0.73
Platelet count (10^3/µl)	1140 ± 64.54	1261 ± 113.3	1005 ± 77.93	1018 ± 62.90
Differential Leucocyte Count				
Neutrophils %	16.03 ± 0.77	17.17 ± 1.75	14.44 ± 1.78	13.08 ± 0.93
Lymphocytes %	74.86 ± 1.28	74.00 ± 1.03	80.50 ± 1.02	75.14 ± 1.61
Monocytes %	5.43 ± 0.65	4.50 ± 0.46	6.22 ± 1.44	6.18 ± 0.87
Eosinophils %	3.56 ± 0.16	4.23 ± 0.99	2.62 ± 0.62	2.46 ± 0.94
Basophils %	0.28 ± 0.09	0.16 ± 0.03	1.22 ± 0.60	0.14 ± 0.02

*The values are expressed as mean ± SD n=5 in each group. *p<0.05 as compared to control at the same time (one-way ANOVA followed by Dunnett's multiple comparison test).*

Bio-chemistry Parameters

The results of bio-chemical parameters did not show any significant change in the group treated with Majoon-IQ when compared to the respective control groups (Table 5).

Table 5: Bio-chemical Parameters of Rats in Acute Oral Toxicity Study

Parameter	Male		Female	
	Control (Mean±SD)	Treated (Mean±SD)	Control (Mean±SD)	Treated (Mean±SD)
Liver Function Tests				
ALT (IU/l)	60.98 ± 5.18	69.63 ± 2.68	66.36 ± 2.42	67.64 ± 3.75
AST (IU/l)	121.1 ± 9.54	122.3 ± 4.60	117.7 ± 4.57	115.7 ± 8.20

ALP (IU/l)	174.2 ± 21.06	164.3 ± 14.38	169.4 ± 12.66	181.2 ± 22.01
Total bilirubin (mg/dl)	0.092 ± 0.01	0.097 ± 0.01	0.096 ± 0.005	0.082 ± 0.01
Total protein (g/dl)	7.39 ± 0.18	6.93 ± 0.13	7.93 ± 0.13	6.76 ± 0.13
Albumin (g/dl)	4.27 ± 0.04	4.37 ± 0.15	4.49 ± 0.10	4.01 ± 0.07
Kidney Function Tests				
Urea (mg/dl)	50.50 ± 1.41	45.83 ± 2.38	50.98 ± 1.48	45.38 ± 2.65
Uric Acid (mg/dl)	2.86 ± 0.33	2.82 ± 0.23	2.80 ± 0.13	2.03 ± 0.34
Creatinine	0.52 ± 0.02	0.44 ± 0.01	0.53 ± 0.01	0.45 ± 0.01
Metabolic Function Tests				
Glucose (mg/dl)	101.6 ± 16.01	104 ± 2.86	105.1 ± 13.76	105.8 ± 6.44
Cholestrol (mg/dl)	57.40 ± 2.70	56.00 ± 3.05	60.80 ± 2.28	65.40 ± 3.23
Triglyceride (mg/dl)	90.6 ± 4.26	86.33 ± 3.84	102.4 ± 13.25	96.80 ± 5.94
HDLC	29.68 ± 0.98	27.30 ± 0.10	37.66 ± 1.45	29.55± 1.60

*The values are expressed as mean ± SD n=5 in each group. *p<0.05 as compared to control at the same time (one-way ANOVA followed by Dunnett's multiple comparison test).*

Sub-Acute Oral Toxicity Test

Group Mean Body Weight (At 4800 mg/kg)

The body weight of rats treated with Majoon-IQ at the dose of 4800mg/kg was found to increase normally as compared to the control rats as shown in Table 6.

Table 6 : Body Weight of Rats in Sub Acute Oral Toxicity Study

Group	Days				
	Day 0 Mean ± SD	**Day 7 Mean ± SD**	**Day 14 Mean ± SD**	**Day 21 Mean ± SD**	**Day 28 Mean ± SD**
Male Control	118.4 ± 7.4	160 ± 2.8	183 ± 4.6	185.8 ± 3.7	216.4 ± 5.6
Male Treated	128.4 ± 6.1	160.2 ± 11.9	180.8 ± 14.5	196.4 ± 19.5	205.6 ± 21.0
Female Control	119.2± 5.8	143.4 ± 8.9	161.8 ± 8.6	170.2 ± 9.6	183.6 ± 8.1
Female Treated	128.7 ± 1.8	155.5 ± 3.4	168.2 ± 5.1	182.7± 5.9	184 ± 8.5

*The values are expressed as mean ± SD n=5 in each group. *p<0.05 as compared to control at the same time (one-way ANOVA followed by Dunnett's multiple comparison test).*

Average Food and Water Consumption (At 4800 mg/kg)

The average feed consumption of both treated groups was found to be unaffected by Majoon-IQ treatment compared to control group rats. No significant decrease in the average water consumption of treated rats was found when compared to the respective controls as shown in Table 7.

Table 7: Average Feed and Water Consumption by Rats

Group Mean Food consumption per rat/24 hours (Grams)				Group Mean Water Consumption per rat/24 hours (Millilitre)	
	Male (Mean±SD)	Female (Mean±SD)		Male (Mean±SD)	Female (Mean±SD)
Control	19.7 ± +1.5	18.3 ± 2.5		29.3 ± 3.05	29.3 ± 5.03
Treated	19.6 ± 1.5	17.5 ± 0.25		27.6 ± 1.4	27.3 ± 2.5

*The values are expressed as mean ± SD n=5 in each group. *p<0.05 as compared to control at the same time (one-way ANOVA followed by Dunnett's multiple comparison test).*

Haematological Parameters (At 4800 mg/kg)

No significant change was observed in the haematological parameters of Majoon-IQ treated rats as compared to the control group rats as indicated in Table 8.

Table 8: Haematological Parameters of Rats in Sub-acute Oral Toxicity Study

Parameter	Male		Female	
	Control (Mean±SD)	Treated (Mean±SD)	Control (Mean±SD)	Treated (Mean±SD)
WBC (10^3/µl)	12.08 ± 5.03	10.50 ± 3.57	10.4 ± 2.07	11.15 ± 3.10
RBC (10^3/µl)	8.49 ± 0.50	8.92 ± 0.90	8.60 ± 0.20	7.98 ± 0.82
Hb (grams %)	16.34 ± 0.90	16.4 ± 1.2	16.7 ± 0.70	15.25 ± 1.64
HCT (%)	49.10 ± 2.9	49.1 ± 3.6	50.3 ± 1.7	45.9 ± 4.2
MCV (Femtolitre)	57.8 ± 3.3	55.2 ± 2.7	58.4 ± 1.6	57.6 ± 2.1
MCH (pico grams)	19.2 ± 0.90	18.4 ± 0.60	19.44 ± 0.30	19.10 ± 0.78
MCHC (grams%)	33.2 ± 0.40	33.4 ± 0.60	33.2 ± 0.60	33.1 ± 0.62
Reticulocytes (%)	4.38 ± 1.12	3.8 ± 0.50	4.1 ± 1.02	4.4 ± 1.55
Platelet count (10^3/µl)	1149 ± 187.3	1235 ± 138	1138 ± 144.8	1108.2± 106
Differential Leucocyte Count				
Neutrophils %	14.1 ± 1.9	15.9 ± 2.55	13.1 ± 4.90	13.3 ± 2.23
Lymphocytes %	79.8 ± 10.7	73.9 ± 8.4	78.3 ± 4.60	79.1 ± 2.40
Monocytes %	3.6 ± 1.01	6.7 ± 3.3	5.7 ± 1.4	5.4 ± 1.17
Eosinophils %	1.8 ± 0.90	1.16 ± 0.92	1.54 ± 0.9	1.6 ± 1.36
Basophils %	0.46 ± 0.23	0.16 ± 0.08	0.48 ± 0.22	0.50 ± 0.73

*The values are expressed as mean ± SD n=5 in each group. *p<0.05 as compared to control at the same time (one-way ANOVA followed by Dunnett's multiple comparison test).*

Bio-chemistry Parameters (At 4800mg/kg)

The bio-chemical parameters of rats treated with 4800mg/kg b.w. of Majoon-IQ showed no significant change as compared to the bio-chemical parameters of control group rats as shown in Table 9.

Table 9: Bio-chemical Parameters of Rats in Sub-acute Oral Toxicity Study

Parameter	Male		Female	
	Control (Mean±SD)	Treated (Mean±SD)	Control (Mean±SD)	Treated (Mean±SD)
Liver Function Tests				
ALT (IU/l)	93.20 ± 13.2	91.80 ± 18.09	93.04 ± 14.6	96.2 ± 25.1
AST (IU/l)	102.3 ± 19.7	106.7 ± 15.7	109.4 ± 20.1	107.8 ± 13.04
ALP (IU/l)	183.8 ± 34.5	187 ± 78.30	179.20 ± 21	170.5 ± 15.43
Total bilirubin (mg/dl)	0.07 ± 0.014	0.08 ± 0.005	0.07 ± 0.01	0.09 ± 0.02
Total protein (g/dl)	8.2 ± 0.36	7.8 ± 0.5	8.05 ± 0.2	8.3 ± 0.34
Albumin (g/dl)	4.30 ± 0.15	4.50 ± 0.14	4.5 ± 0.10	4.30 ± 0.80
Kidney Function Tests				
Urea (mg/dl)	47.00 ± 3.7	50.6 ± 8.5	46.3 ± 6.01	51.7 ± 13.4
Uric Acid (mg/dl)	2.2 ± 0.61	2.2 ± 0.23	2.7 ± 0.70	2.1 ± 1.05
Creatinine	0.50 ± 0.01	0.50 ± 0.05	0.50 ± 0.01	0.50 ± 0.05
Metabolic Function Tests				
Glucose (mg/dl)	106.6 ± 13.2	99.8 ± 19.6	97.5 ± 21.4	107.0 ± 19.9
Cholestrol (mg/dl)	53.60 ± 6.5	48.90 ± 7.6	57.40 ± 3.36	56.00 ± 12.51
Triglyceride (mg/dl)	86.80 ± 12.2	82.40 ± 29.80	94.60 ± 31.0	94.25 ± 40.55
HDLC	31.34 ± 6.89	24.92 ± 2.03	36.16 ± 3.58	35.92 ± 11.51

*The values are expressed as mean ± SD n=5 in each group. *p<0.05 as compared to control at the same time (one-way ANOVA followed by Dunnett's multiple comparison test).*

Relative Organ Weight of Treated and Controls

No significant change in the relative organ weights of Majoon-IQ treated rats was observed (Table 10)

Table 10 : Relative Organ Weight of Rats in Sub-acute Oral Toxicity Study

Organ	Male (control) (Mean ±SD)	Male (treated) (Mean ±SD)	Female (control) (Mean ±SD)	Female (treated) (Mean ±SD)
Brain	1.7±0.05	1.5±0.07	1.5±0.07	1.6±0.07
Spleen	0.6±0.007	0.5±0.06	0.7±0.02	0.7±0.15
Rt Adrenal	0.03±0.0	0.03±0.0	0.02±0.0	0.02±0.0
Lt Adrenal	0.03±0.0	0.03±0.0	0.02±0.001	0.03±0.001
Heart	0.81±0.18	0.71±0.06	0.68±0.07	0.66±0.02
Lung	1.51±0.2	1.42±0.13	1.31±0.05	1.42±0.05
Rt kidney	0.9±0.11	0.66±0.04	0.68±0.07	0.70±0.03

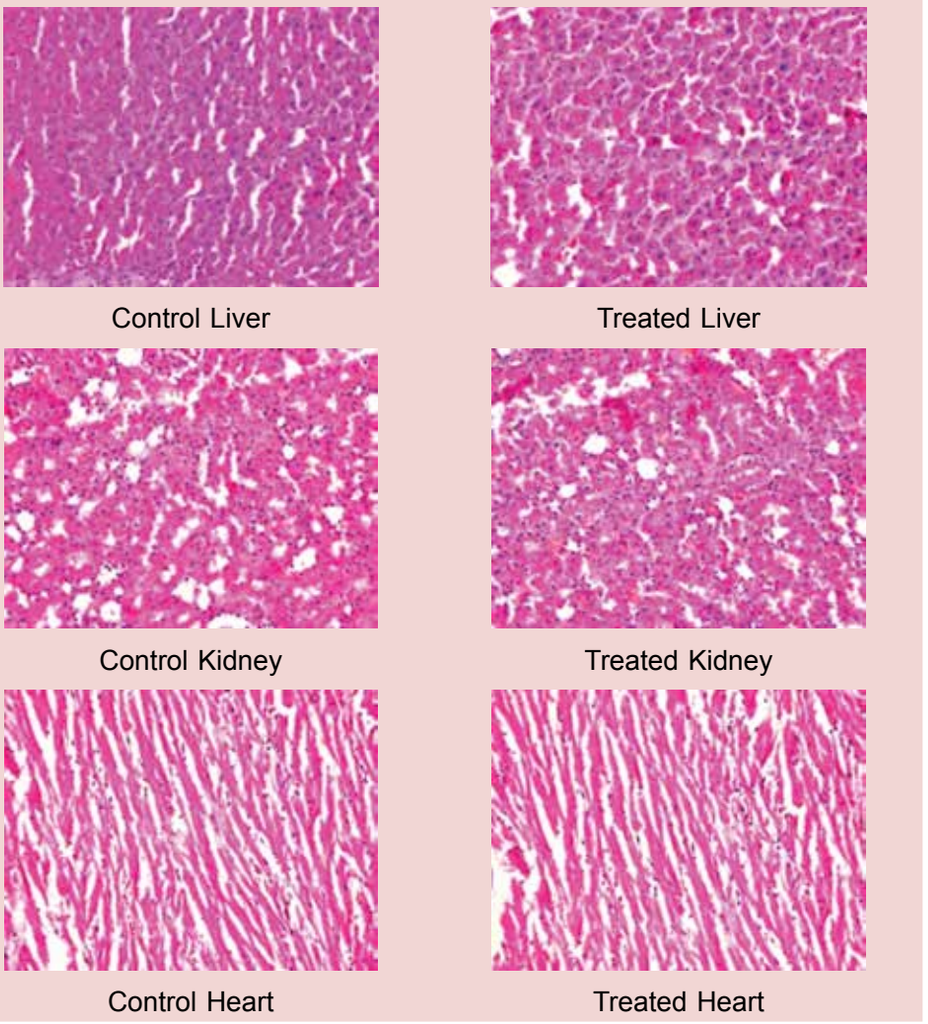
Lt kidney	0.9±0.12	0.66±0.03	0.66±0.04	0.68±0.05
Rt testis/Ovary	1.2±0.12	0.7±0.43	0.06±0.07	0.045±0.07
Lt testis/Ovary	1.2±0.09	0.7±0.31	0.06±0.04	0.05±0.14
Liver	7.12±2.3	6.74±0.007	6.25±0.42	6.85±0.2
Pancreas	0.52±0.12	0.47±0.16	0.44±0.08	0.42±0.11

*The values are expressed as mean ± SD n=5 in each group. *p<0.05 as compared to control at the same time (one-way ANOVA followed by Dunnett's multiple comparison test).*

Histopathological Parameters

The histopathological examination of the treated animals also indicated that there was no damage to the tissues/organs when compared to the control animals as shown below:

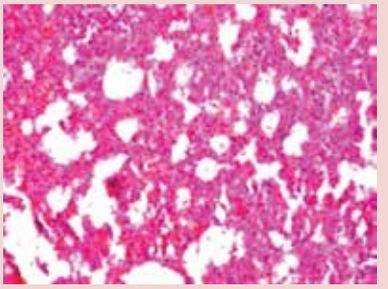
Histopathology of Control and Treated Rats



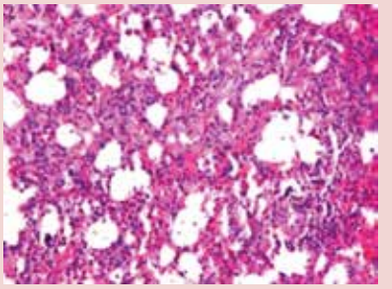
Control Liver | Treated Liver

Control Kidney | Treated Kidney

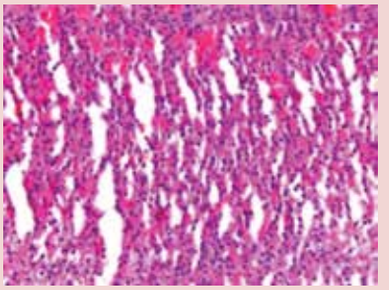
Control Heart | Treated Heart



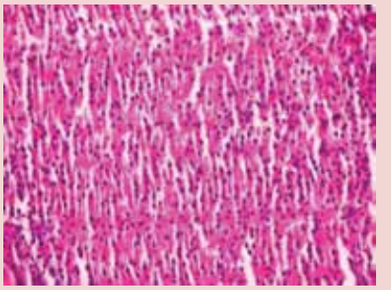
Control Lung



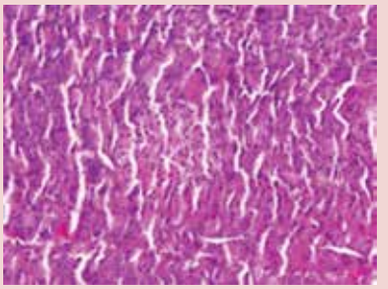
Treated Lung



Control Adrenal



Treated Adrenal



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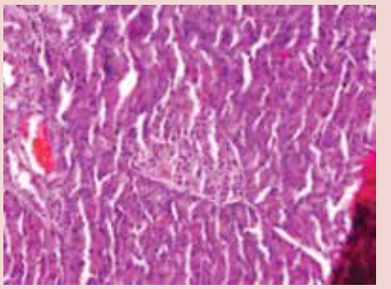

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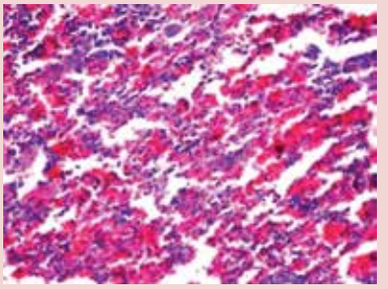

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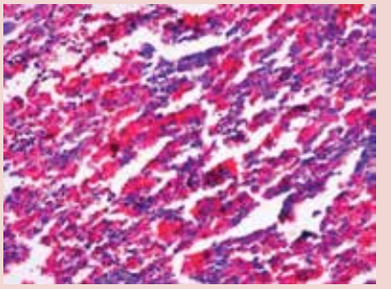

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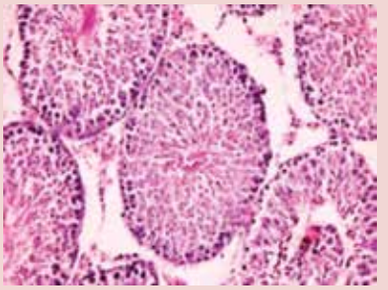
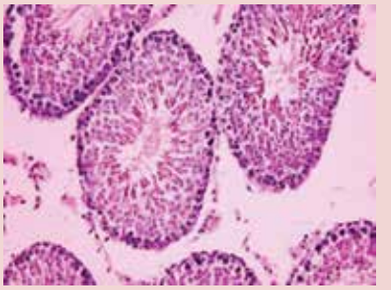


Control Testis



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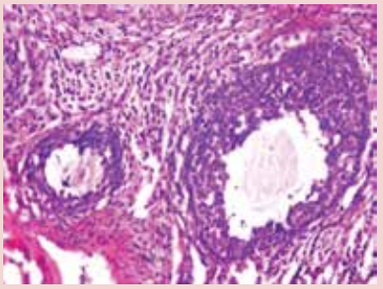
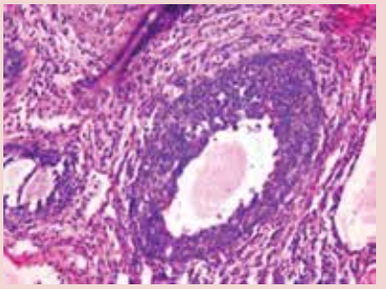
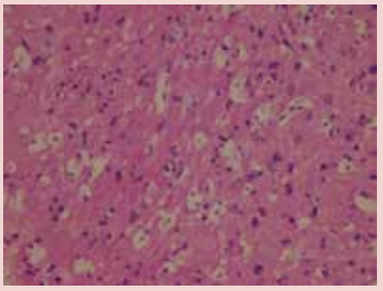


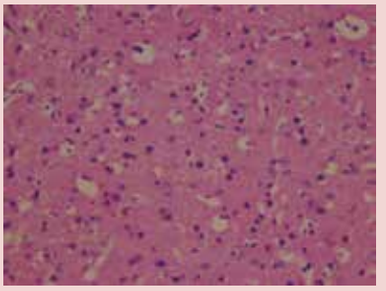
Control Ovary



Treated Ovary



Control Brain



Treated Brain

Discussion and Conclusion

With the enormous global consumption of herbal medicines, it is high time that they are included in pharmacovigilance systems. In terms of population exposure alone, it is essential to identify the risks associated with the use of herbal medicine and in this regard, the safety of these products has become an issue of great public health importance (WHO, 2004, 2005b). There is no doubt that the increasing cases of poisoning associated with use of herbal medicines in many parts of the world in recent times is necessitating the need to ensure thorough toxicity assessment alongside active pharmacovigilance on these products in order to promote their safe use and protect public health (Zhou *et al.,* 2013). In view of the above facts the acute and sub-acute oral toxicity study of Majoon-IQ was undertaken.

Acute Oral Toxicity Study

The drug Majoon-IQ was found to have no negative effect on the body weight gain of the treated male and female rats. The treated rats were found to grow normally. There was no significant change in the feed and water consumption of the treated male and female rats when compared to the respective controls. The gross behaviour of rats was not changed by the drug administration as no significant change was found in the parameters observed. Blood bio-chemical and haematological parameters were also normal. Gross examination of the organs and tissues did not reveal any treatment-related differences in the treated groups.

Sub-acute Oral Toxicity Study

The male and female treated rats were found to have a normal weight gain. There were no signs of abnormal behaviour in the treated rats. There was a slight

decrease (Statistically insignificant) in the average water consumption per day by the male and female rats treated with the drugs as compared to the respective controls. The drug was found to have no effect on the average feed consumption by the drug treated rats. Gross examination of the tissues revealed the normal appearance of the tissues/organs. The results of bio-chemical parameters did not show any significant change in the values when compared to the controls. The liver and kidney function tests were found to be normal in the drug treated groups. The lipid profile of the drug treated male and female rats was found to be unaffected when compared to the respective controls. The blood parameters were unaffected by the drug as the values of drug treated rats are within the range of control rats. No treatment related morphological changes were observed in the vital organs such as brain, heart, lung, liver, kidney, spleen, adrenal, testes and ovaries of the rats at the dose level tested. There was also no significant difference observed in the organ weights of male and female treated rats when compared to the respective controls.

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सारांश

माजून-ए-आईक्यू का तीव्र एवं उप-तीव्र मौखिक विषाक्तता अध्ययन - एक यूनानी दिमागी शक्ति वर्धक औषधि

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माजून–ए–आईक्यू एक यूनानी जड़ी–बूटी औषधि है जिसका प्रयोग दिमागी शक्ति वर्धक टॉनिक के रूप में किया जाता है। इस अनुसंधान का मुख्य उद्देश्य माजून–ए–आईक्यू की तीव्र और उप–तीव्र मौखिक विषाक्तता का विस्तार अलबिनो चूहों की दोनों जाति (नर व मादा) में अध्ययन करना था। तीव्र मौखिक विषाक्तता का अध्ययन आईसीडी–425 दिशा–निर्देशों के अनुसार किया गया। इस अध्ययन में माजून–ए–आईक्यू दवा को 5000 मिलीग्राम/किलोग्राम नर और मादा चूहों के शरीर के वजन के स्तर के अनुसार दी गई। इसके पश्चात् चूहों को 30 मिनट के लिए, खुराक के चार घंटे बाद और अगले 14 दिनों तक दिन में कम से कम दो बार व्यक्तिगत रूप से निरीक्षण किया गया। चूहों में उप तीव्र मौखिक विषाक्तता का अध्ययन आईसीडी–407 के दिशा–निर्देशों के अनुसार किया गया। इस अध्ययन में माजून–ए–आईक्यू औषधि की खुराक चूहों के शरीर के वजन के अनुसार 4800 मिलीग्राम/किलोग्राम की अस्तत मात्रा को 28 दिनों के लिए प्रतिदिन दिया गया एवं अनुसंधान अवधि के दौरान प्रतिदिन चूहों का निरीक्षण किया गया। एक रात उपवास के बाद चूहों को 15वें और 29वें दिन अनुसंधान करने के लिए मार दिया गया। निरीक्षण मानदंडों में सामान्य उपस्थिति/व्यवहार, रूग्णता(अस्वस्थता)/मृत्यु–दर, शरीर का वज़न, भोजन/पानी की खपत, रक्त–रोग मापदंड, जैव–रसायनिक मापदंड आदि का तुलनात्मक मूल्यांकन किया गया। चूहों में किसी प्रकार की मृत्यु–दर, रूग्णता एवं प्रायोगिक जाँच में दोनों तीव्र और उप–तीव्र मौखिक विषाक्तता नहीं पाई गई। इस अनुसंधान अध्ययन से यह पता चलता है कि माजून–ए–आईक्यू किसी भी प्रकार की विषाक्तता से मुक्त है।