Acute oral toxicity studies of *Swietenia macrophylla* seeds in Sprague Dawley rats

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Submitted: 15-05-2014 Revised: 08-07-2014 Published: 17-12-2014

ABSTRACT

Background: *Swietenia macrophylla* King. (Meliaceae) seeds (SMS); commonly known as sky fruit and locally known in Malaysia as Tunjuk Langit; have been used in traditional Malay medicine for the treatment of diabetes and hypertension. The people eat only a tiny amount of raw seed, weighing not more than 5 mg. **Aim:** To evaluate the safety of *Swietenia macrophylla* seeds (SMS) at a single-dose oral administration of 2 g/kg body weight (bw) in sprague dawley (SD) rats. **Materials and Methods:** Eight-week old male and female SD rats were administered a single-oral dose of 2g/kg bw. The rats' general behavior, and toxic signs were observed throughout the 14-day study period. The food and water intake by rats and their body weight were monitored during the study period. At the end of the study period, the relative weights of the organs (lung, liver, spleen, heart, kidney, testis, stomach); the hematological and biochemical parameters were measured; the architecture and histology of the organs (liver, kidney and lungs) were observed. **Results:** Oral administration of SMS to rats did not affect, either food or water intake; relative organ weight of vital organs; the hematological and biochemical parameters; did not show significant changes in the architecture and histology of vital organs. Overall, there were neither signs of toxicity nor deaths recorded during the study period. **Conclusion:** The rat dose of 2 g/kg bw is equivalent to the human dose of 325 mg/kg bw, which is well below the usual amount consumed by people, did not show any signs of toxicity in rats.

Key words: Diabetes, sky fruit, *Swietenia macrophylla,* toxicity, traditional Malay medicine, tunjuk langit

Access this article online

Website: www.phcogres.com

DOI: 10.4103/0974-8490.147197

Quick Response Code:

INTRODUCTION

Swietenia macrophylla King (Meliaceae) is a tall, lofty, evergreen tree found in tropical vicinities of the world. Its fruit is colloquially known as "sky fruit" as it appears to point toward the sky and in Malaysia, is known as "Tunjuk Langit". Various parts of *Swietenia macrophylla* have been used to treat a great array of ailments in various traditional and folk-lore systems of medicine. The seeds in particular are purported to have ethno medicinal significance against numerous diseases running the gamut from treatment of leishmaniasis and abortion by an Amazonian Bolivian group, through to folk medicine in Indonesia, Malaysia and India for the treatment of wounds, hypertension, diabetes and malaria.[1,2]

Swietenia macrophylla has been reported to possess hypoglycaemic,[3-5] antimicrobial,[3,6,7] antimalarial[8] and antiviral[9] activities. *Swietenia macrophylla* is a good source of bioactive tetranorterpenoids, phargmalin-type limonoids.[10-20]

In Malaysia, the raw seeds have been used as a folk-lore medicine for the treatment of hypertension and diabetes. Despite the wide use of raw *Swietenia macrophylla* seeds in folk-lore medicine, there were no data on the safety

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of consuming its raw seeds for these claims. This present study was undertaken to provide scientific data on the safety focusing on the acute toxicity of *Swietenia macrophylla* seeds powder given orally to Sprague Dawley (SD) rats. The usual way to determine whether the plants are safe for human consumption is by evaluating the toxic effects of respective extracts. However, in this study, we have attempted to evaluate the acute toxicity of raw *Swietenia macrophylla* seeds without any extraction, to mimic the way humans have consume them.

MATERIALS AND METHODS

Plant material and extraction

Swietenia macrophylla seeds (SMS) collected in the months of November and December, 2011 from Agricultural Conservatory Park, Universiti Putra Malaysia (UPM) were used in the study. The plant was authenticated by Dr. Shamsul Khamis, Coordinator, Biodiversity Unit, Institute of Bioscience (IBS), UPM. A voucher specimen (SK247/02) was deposited at Institute of Bioscience, UPM. SMS were grounded to a fine powder using a domestic blender and suspended in olive oil for evaluating its acute toxicity.

Experimental animals

Eight-week-old male and female SD rats with weight range of 150 to 220 g obtained from Universiti Putra Malaysia animal house were used in the study. All animal experimentations were in accordance to the guidelines of "Handling of Laboratory Animals" by Ministry of Health Malaysia.[21] The study protocol was approved by the Institute Research and Ethics Committee, International Medical University (IMU), with a project ID number BMS I-01/2012 (11). The animals were housed in the Animal House, IMU. The rats were housed individually per cage and acclimatised for a week prior to the start of the study. An environment with room temperature of 27°C and 12 h of alternate light and dark cycle was maintained throughout the experiments. The rats were given unlimited supply of water and standard diet.

Acute toxicity study

The rats were assigned randomly to the control and treatment groups. In each group there were 20 rats out of which 10 rats were male and the remaining 10 rats were female. The treatment group were given oral administration, using an intubation needle, of SMS at a single dose of 2 g/kg body weight (bw) suspended in olive oil while the control group received olive oil. The animals were observed for toxic effects and the body weight was recorded daily throughout the 14-day study period. The rats were observed twice daily for toxic signs, *viz.*, changes in skin, fur, eyes; occurrence of secretions and excretions, autonomic activity, changes in gait, posture, response to handling, presence of tonic movements (e.g. excessive grooming, repetitive circling) and bizarre behavior (e.g. self-mutilation, walking backwards).

All the rats were weighed once prior to administration of the dosing and daily thereafter till the final day of the experiment. On Day 14, blood sample was collected from each rat under ether anaesthesia. Half the volume of blood was collected in a tube containing anticoagulant (EDTA) and remaining half the volume in another tube without anticoagulant. The blood samples with anticoagulant were analysed using Sysmex, KX-21N (Sysmex Cooperation, Japan) to obtain hematological parameters. The serum was taken from the blood samples without anticoagulant and were analyzed using Vitalab Selectra, E-series (Netherlands) to obtain biochemical parameters. The animals were sacrificed by an overdose of ether and the rats were dissected to obtain the organs *viz.*, lungs, liver, spleen, heart, kidneys, testis, stomach; for further examination and each organ's weight (absolute organ weight in g) was recorded.

Using the following formula, the relative organ weight (ROW) of each organ was calculated:

$$\text{ROW} = \frac{\text{Absolute organ weight (g)}}{\text{Body weight of rat on the day of sacrifice (g)}} \times 100$$

Histopathological evaluation

Necropsy was performed on all animals at the end of the study. All rats were killed by ether anaesthesia after recording the terminal body weights. The organs (lungs, liver, spleen, heart, kidneys, testis, and stomach) were fixed and stored in a 10% neutral buffered formaldehyde solution at room temperature until further analysis. The tissues were sliced laterally and longitudinally in order to place them into the cassettes. The tissues were then processed in Leica rotary microtome (model, RM 2135) in which the tissues were run through formalin, followed by a series of graded ethanol, xylene and paraffin wax. After processing overnight, the tissues were embedded in molten paraffin. Paraffin sections were cut at 4 μm of thickness, mounted on glass slides and left to air-dry. Briefly, paraffin sections were heated at 60°C for 45 min. The paraffin sections were deparaffinised in xylene, and rehydrated in a graded series of alcohol (two changes of absolute ethanol to xylene, one change of 90% ethanol, one change of 80% ethanol and one change of 70% ethanol) with a final wash in running tap water for 10 min. Each

change was approximately 5 min. The sections were then stained with hematoxylin for 30 min followed by eosin. After completion of the staining, sections were dehydrated by sequential immersion in water, through graded ascending alcohol solutions (70%, 80%, 90% and 100% ×2) and two changes of xylene. Then it was followed by mounting of the stained tissues using DPX, rendering them suitable for light microscopy examination. The sections were viewed and photographed on a Nikon Eclipse 80i Fluorescence microscope with attachment of Nikon DS 5MC-U2 camera using NIS-elements BR software. Histological changes in vital organs, *viz.,* testis, liver, kidney, heart, stomach, lung and spleen; in rats were graded on a scale of 0-9, based on the nature and severity of histological changes. The scoring system employed for assessing the histological changes as follows: Score 0 indicates preservation of normal architecture and histology, A1-degeneration of architecture in ≤20% cells, A2-degeneration of architecture in 21-50% cells, A3-degeneration of architecture in >50% cells, I1-minimal inflammation, I2-small localized inflammation, I3-diffused inflammation, N1-necrotic foci in few cells at one location, N2-necrotic foci at different locations and N3-diffuse necrosis.

Statistical analysis

Statistical analysis for each parameter was performed to obtain the mean value and standard deviation. Statistical Package for Social Science (Version 18.0) was used to obtain ANOVA for repeated measurements to analyse the effect of SMS. Results with $P < 0.05$ was considered as statistically significant.

RESULTS

To assess the acute toxic effects of SMS, 2 g/kg bw dose was orally given to male and female rats. All animals in the treatment and control groups showed an increase in the body weight on day-7 and day-14 compared to day-0 [Table 1]; however the increase in body weight was not statistically significant. It was observed that the average water intake [Table 2] by rats in treated group is high during week-1 and restored back to normal levels during week-2 of the acute toxicity study as compared to control group. The food consumed [Table 2] by rats in treated group is low during week-1 and restored back to normal levels during week-2 of the acute toxicity study as compared to control group. Neither mortality nor alteration in the behavioral pattern of the rats was noted. Overall, the animals treated with SMS showed no significant changes in the food and water intake behavior. The ROW of the lungs, livers, spleens, hearts, testes and stomachs of the rats in the treatment group showed no significant changes as compared with the control group [Table 3]. The hematological [Table 4] and biochemical parameters [Table 5] were within the range of the control animals and the mean values between the groups were not statistically significant. These data collectively indicate that SMS did not affect the vital organs and hematological and biochemical parameters. Examinations of the architecture of the major organs such as lungs, liver, spleen, heart, kidneys, testis, and stomach were conducted. The macroscopic examination did not show any significant changes in the vital organs of treated rats compared with the

Table 1: Summary of rats' body weights recorded during the acute toxicity study of SMS

Group	Dose	Body weight (g)					
		Day 0		Day 7		Day 14	
		Male	Female	Male	Female	Male	Female
Control (olive oil)	2 mL/kg	217.68±18.67	226.98±25.31	224.65±6.54	230.72±12.48	227.77±5.23	231.17±18.72
Treatment (SMS)	2 g/kg	214.56±21.48*	230.54±24.89*	219.32±13.27*	232.05±6.57*	220.03±15.29*	231.69±13.23*

The values represent the mean±standard deviation from n=10; *P>0.05, no significant change compared with the respective control. SMS=*Swietenia macrophylla* seeds

Table 2: Summary of rats' water intake (ml/rat.day) and feed consumed (g/rat.day) recorded during the acute toxicity study of SMS

Group	Dose	Week 1		Week 2	
		Male	Female	Male	Female
Water intake					
Control (olive oil)	2 mL/kg	79.35±16.48	83.67±19.64	81.26±19.86	79.65±18.20
Treatment (SMS)	2 g/kg	112.65±32.56**	129.68±40.28**	95.63±24.59*	92.31±27.81*
Food consumed					
Control (olive oil)	2 mL/kg	135.28±26.30	128.97±34.29	140.27±31.43	132.08±29.97
Treatment (SMS)	2 g/kg	110.08±19.67**	92.56±24.79**	138.97±21.08*	135.96±41.29*

The values represent mean±standard deviation from n=10; water intake is measured as number of millilitres of water consumed per rat per day; food consumed is measured as number of grams of food consumed by each rat per day; *P>0.05, no significant change compared with the respective control; **P<0.05, significant change compared with the respective control. SMS=*Swietenia macrophylla* seeds

control rats, indicating that SMS was not toxic to rats. To further assess the tissue toxicity, microscopic examination of histological preparations of selected vital organs (lungs, liver, spleen, heart, kidneys, testis, and stomach) was performed. Scoring of pathological changes revealed that the SMS did not induce significant changes compared with the control animals [Table 6]. Examples of photomicrographs of histology of liver, kidney and lung are shown in Figure 1. The liver showed minimal and mild inflammation with few scattered inflammatory cells and focal inflammatory infiltrates. However, this finding was not considered significant as this phenomenon was also observed in all rats of both control and treated groups. There were no histological changes observed in the kidneys and lungs, with both organs showing a preserved normal architecture. The SMS powder had no apparent acute toxicity effect on SD rats at selected dose, 2 g/kg bw and therefore can be classified as non-toxic.

Table 3: Summary of rats' relative organ weights (per 100 g body weight) calculated at the end of acute toxicity study of SMS

Organ	Control (olive oil, 2 mL/kg)		Treatment (SMS, 2 g/kg)	
	Male	Female	Male	Female
Lung	0.79±0.13	0.75±0.05	0.75±0.06*	0.79±0.12*
Liver	3.71±0.48	3.37±0.33	3.13±0.21*	3.36±0.49*
Spleen	0.31±0.10	0.24±0.03	0.26±0.06*	0.27±0.07*
Heart	0.38±0.05	0.41±0.09	0.36±0.04*	0.42±0.08*
Kidney	0.87±0.12	0.76±0.08	0.77±0.07*	0.78±0.10*
Testis	1.07±0.13	NA	1.04±0.12*	NA
Stomach	1.16±0.39	1.40±0.23	1.25±0.28	1.40±0.40*

The values represent mean±standard deviation from *n*=10; **P*>0.05, no significant change in the relative organ weight compared with the respective control; relative organ weights were measured at the end of acute toxicity study. SMS=*Swietenia macrophylla* seeds

Table 4: Summary of rats' haematological parameters measured at the end of acute toxicity study of SMS

	Control (olive oil, 2 mL/kg) (*n*=10)		Treatment (SMS, 2 g/kg) (*n*=10)	
	Male	Female	Male	Female
WBC (x10^3/µL)	12.90±3.17	8.00±3.18	10.60±2.92*	9.60±5.61*
RBC (x10^6/µL)	7.13±1.09	6.97±0.70	7.27±0.30*	7.32±1.44*
HGB (g/dL)	14.01±2.23	12.58±1.11	13.65±0.54*	14.56±3.68*
HCT (%)	43.0±7.0	39.0±4.0	42.0±2.0*	40.0±3.0*
MCV (fl)	59.82±2.85	55.30±2.05	58.18±1.55*	58.08±1.06*
MCH (pg)	19.66±0.94	18.16±1.64	18.78±0.58*	19.77±1.06*
MCHC (g/dL)	32.91±0.89	32.83±2.86	32.26±0.57*	34.00±1.67*
PLT (x10^3/µL)	521±247	548±480	626±215*	454±282*
LYM (%)	71±12	78±6	68±7*	75±4*

The values represent mean±standard deviation from *n*=10; **P*>0.05, no significant change compared with the respective control; hematological parameters were measured at the end of acute toxicity study. WBC=White blood cells, RBC=Red blood cells, HGB=Hemoglobin, HCT=Hematocrit, MCV=Mean corpuscular volume, MCH=Mean cell haemoglobin, MCHC=Mean corpuscular haemoglobin concentration, PLT=Platelet, LYM=Lymphocytes, SMS=*Swietenia macrophylla* seeds

DISCUSSION AND CONCLUSION

Majority of the people in rural areas of Malaysia have been consuming medicinal plants for the treatment of various illnesses; especially chronic diseases like diabetes, hypertension, arthritis etc. However, evidence of safety of SMS reported in the literature is limited. Therefore, toxicology studies are important to determine the safe dose for human consumption.

In order to find the equivalent safe dose of SMS for human consumption, we have calculated the human equivalent dose (HED) using the following formula; which is developed based on the body surface area (BSA) normalization method; reported in the literature.[22]

$$\text{HED}(\text{mg/kg}) = \text{ratdose}(\text{mg/kg}) \times \frac{K_m \text{ factor for rat}}{K_m \text{ factor for human adult}}$$

$$\text{HED}(\text{mg/kg}) = 2000 \times \frac{6}{37} = 324.32\,\text{mg/kg}$$

Table 5: Summary of rats' biochemical parameters measured at the end of acute toxicity study of SMS

	Control (olive oil, 2 mL/kg)		Treatment (SMS, 2 g/kg)	
	Male	Female	Male	Female
AST (U/L)	5.18±3.72	3.25±1.69	2.19±1.16*	3.37±1.04*
ALT (U/L)	1.11±0.42	1.59±1.85	0.81±0.29*	1.08±0.23*
Urea (mmol/L)	5.67±0.73	6.63±1.06	5.06±1.43*	5.12±1.84*
ALP (U/L)	246.19±88.13	246.19±88.13	164.61±41.73*	134.27±27.42*
Na (mmol/L)	118.93±10.69	123.48±2.63	105.05±4.42*	122.29±6.32*
K (mmol/L)	9.85±4.17	8.80±4.67	7.21±3.01*	8.35±1.36*
Cl (mmol/L)	89.86±8.73	91.35±1.84	83.71±2.75*	95.17±4.94*

The values represent mean±standard deviation from *n*=10; **P*>0.05, no significant change compared with the respective control; biochemical parameters were measured at the end of acute toxicity study. SMS=*Swietenia macrophylla* seeds

Table 6: Summary of rats' histological scores determined at the end of acute toxicity study of SMS

Groups	Dose	Histological score								
		0	Architecture			Inflammation			Necrosis	
			A1	A2	A3	I1	I2	I3	N1	N2	N3
Group A											
Control (olive oil)	2 mL/kg	10	0	0	0	0	0	0	0	0	0
Treatment (SMS)	2 g/kg	10	0	0	0	0	0	0	0	0	0
Group B											
Male											
Control (olive oil)	2 mL/kg	9	0	0	0	1	0	0	0	0	0
Treatment (SMS)	2 g/kg	10	0	0	0	0	0	0	0	0	0
Female											
Control (olive oil)	2 mL/kg	7	0	0	0	3	0	0	0	0	0
Treatment (SMS)	2 g/kg	9	0	0	0	1	0	0	0	0	0
Group C											
Male											
Control (olive oil)	2 mL/kg	8	0	0	0	2	0	0	0	0	0
Treatment (SMS)	2 g/kg	7	0	0	0	3	0	0	0	0	0
Female											
Control (olive oil)	2 mL/kg	9	1	0	0	0	0	0	0	0	0
Treatment (SMS)	2 g/kg	8	0	0	0	2	0	0	0	0	0
Group D											
Male											
Control (olive oil)	2 mL/kg	10	0	0	0	0	0	0	0	0	0
Treatment (SMS)	2 g/kg	10	0	0	0	0	0	0	0	0	0
Female											
Control (olive oil)	2 mL/kg	10	0	0	0	0	0	0	0	0	0
Treatment (SMS)	2 g/kg	10	0	0	0	0	0	0	0	0	0
Group E											
Male											
Control (olive oil)	2 mL/kg	8	0	0	0	2	0	0	0	0	0
Treatment (SMS)	2 g/kg	7	0	0	0	3	0	0	0	0	0
Female											
Control (olive oil)	2 mL/kg	9	0	0	0	1	0	0	0	0	0
Treatment (SMS)	2 g/kg	8	0	0	0	2	0	0	0	0	0
Group F											
Male											
Control (olive oil)	2 mL/kg	10	0	0	0	0	0	0	0	0	0
Treatment (SMS)	2 g/kg	10	0	0	0	0	0	0	0	0	0
Female											
Control (olive oil)	2 mL/kg	10	0	0	0	0	0	0	0	0	0
Treatment (SMS)	2 g/kg	10	0	0	0	0	0	0	0	0	0
Group G											
Male											
Control (olive oil)	2 mL/kg	9	0	0	0	1	0	0	0	0	0
Treatment (SMS)	2 g/kg	10	0	0	0	0	0	0	0	0	0
Female											
Control (olive oil)	2 mL/kg	10	0	0	0	0	0	0	0	0	0
Treatment (SMS)	2 g/kg	9	0	0	0	1	0	0	0	0	0

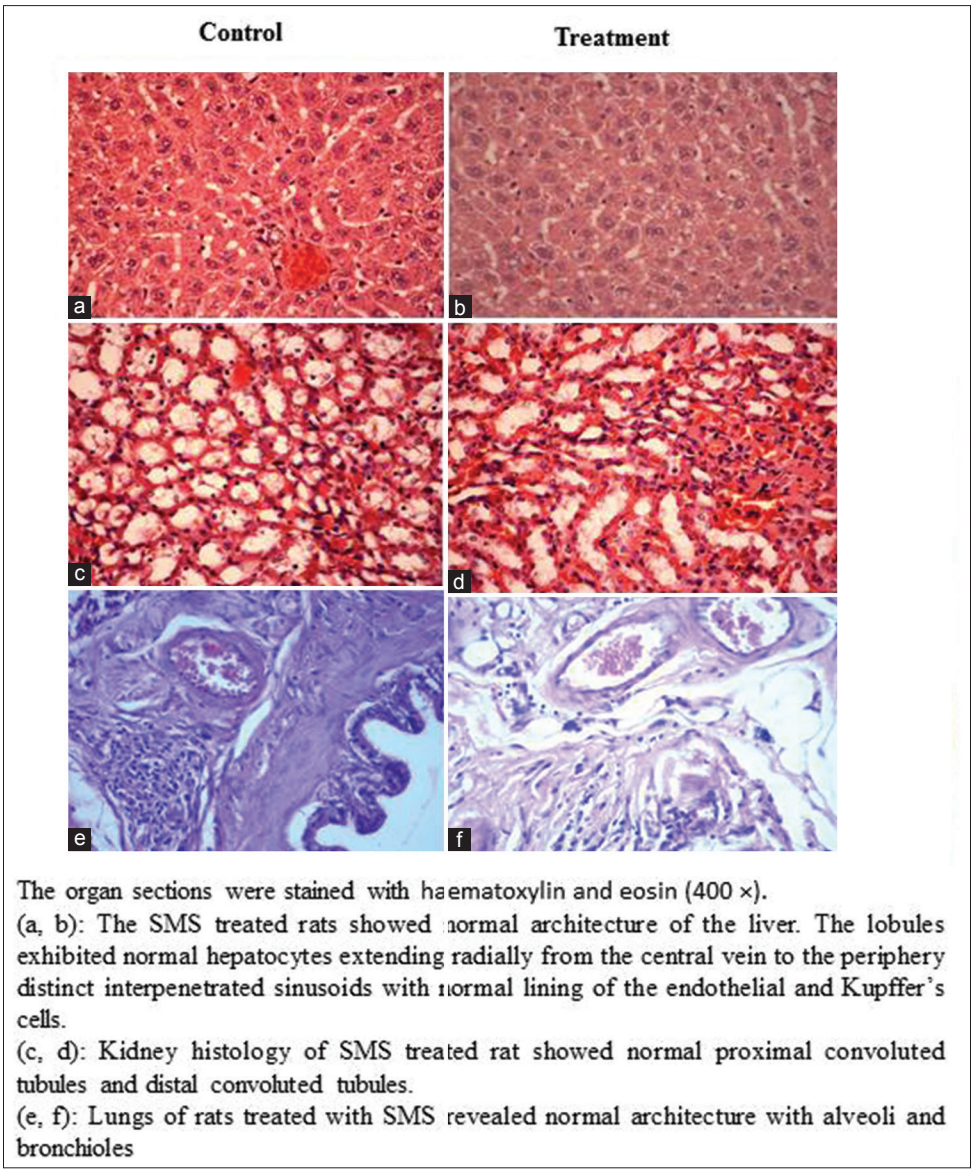
Group A represents the histological scores of male rats' testis; Group B represents the histological scores of rats' liver; Group C represents the histological scores of rats' kidney; Group D represents the histological scores of rats' heart; Group E represents the histological scores of rats' stomach; Group F represents the histological scores of lung; Group G represents the histological scores of rats' spleen. The numeral in each row indicates the number of rats scored a particular histological score. SMS=*Swietenia macrophylla* seeds

From the above calculations, the SMS may be safe until a dose of 325 mg/kg bw for human consumption.

In conclusion, the *Swietenia macrophylla* seeds (SMS) at a single dose of 2 g/kg bw did not show any signs of toxicity in Sprague Dawley rats. Based on these findings, we assume that consumption of SMS by humans is safe if the dose is less than 325 mg/kg body weight. The usual dose of SMS prescribed in Malaysian folk-lore medicine is one seed; weighing about 5 mg per day. Therefore, the prescribed dose of SMS in Malaysian folk-lore medicine is safe for human consumption.

ACKNOWLEDGEMENTS

This study was supported by International Medical University (BMS I-01/2012 (11)); Ministry of Higher Education, Malaysia, FRGS grant (FRGS/1/2014/STWN10/IMU/02/1).



The organ sections were stained with haematoxylin and eosin (400 ×).
(a, b): The SMS treated rats showed normal architecture of the liver. The lobules exhibited normal hepatocytes extending radially from the central vein to the periphery distinct interpenetrated sinusoids with normal lining of the endothelial and Kupffer's cells.
(c, d): Kidney histology of SMS treated rat showed normal proximal convoluted tubules and distal convoluted tubules.
(e, f): Lungs of rats treated with SMS revealed normal architecture with alveoli and bronchioles

Figure 1: Representative photomicro graphs of the sections from the liver (a,b), kidney (c,d) and lungs (e,f) of control and SMS treated male rats

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Cite this article as: Balijepalli MK, Suppaiah V, Chin A, Buru AS, Sagineedu SR, Pichika MR. Acute oral toxicity studies of *Swietenia macrophylla* seeds in Sprague Dawley rats. Phcog Res 2015;7:38-44.

Source of Support: Nil, **Conflict of Interest:** None declared.