

# Safety evaluation of polyherbal Unani formulation -Deedan in Wistar rats

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## ABSTRACT

Unani system of medicine is gaining popularity day by day owing to its efficiency, low cost, availability and to the safety of its formulations and drugs/medicines. The current study was aimed to determine the safety of a polyherbal Unani formulation named Deedan. A suspension of powdered Deedan at the dose of 300mg/kg of b. wt was orally administered to the male and female group of rats (n=5) for 90 days daily and then sacrificed. The biochemical and hematological parameters of treated rats were compared with respective control group of rats. Various vital organs/tissues were collected, examined, weighed and tissue samples were taken for histopathological studies of both the treated and control groups. Physiological parameters like water and feed consumption were also observed in all the groups. The treated rats (both males and females) were found to gain bodyweight normally. There was no effect of the drug on biochemical and hematological parameters as the changes were statistically insignificant. The histopathological studies revealed the normal appearance of tissues. The feed and water consumption in treated group of rats was found to be unaffected by the drug administration. The drug deedan was found to be safe at the dose of 300 mg/kg of body weight when administered orally to the rats for 90 days.

## INTRODUCTION

One of the popular alternative modes of treatment in India is the Unani System of Medicine, emerging as a lead in treating patients in the Indian System of Medicine. In many places, it offers a more wide available and more affordable alternative to pharmaceutical drugs and chemicals. Medicinal plants have occupied a vital place in the sociocultural, development of rural people of India (Fulekar *et al.*, 2006; Patil *et al.*, 2010). There is a tremendous growth in the consumption of its products owing to fact having quality, efficacy, and safety besides being available at lower costs (Verma *et al.*, 2008).

However for Unani drugs and formulations their efficacy is well documented and clinically proved yet their safety evaluation is at large to be undone. To be accepted by the international community the Unani drugs have to satisfy the safety of through contemporary scientific tools; following norms

set by accepted International Regulatory Agencies (Shetti *et al.*, 2011). Safety studies of unani drugs provide scientific justification for their traditional use and prove that they are safe and efficacious. The data of the various toxicity studies on Unani formulations or preparations derived from them should be obtained in order to increase the confidence in its safety to humans (WHO, 2004). When reviewed literature, so far no scientific evaluations were carried out in this drug for its toxicity profile pre-clinically. The purposes of the present study was to investigate the subchronic oral toxicities of the Unani drug- Deedan in rats. Deedan is polyherbal formulation used against various human endoparasites like *Trichuris trichiura* (whipworm), *Enterobius vermicularis* (pinworm) and *Giardiasis* (CCRUM, 2007). Mebendazole is commonly used for the treatment of *Trichuris trichiura*. Albendazole or Mebendazole is the first-line treatment of *Enterobius vermicularis* infection. Albendazole may cause abdominal pain, dizziness, headache, fever, nausea, vomiting, or temporary hair loss. Elevation of liver enzymes during treatment is a common side effect, but in rare cases, acute liver failure has been reported. Allergic reactions are also possible (Zheng *et al.*, 2013; Ben *et al.*, 2014; Albenza, 2011).

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Mebendazole causes diarrhea, abdominal pain, and elevated liver enzymes. In rare cases, it has been associated with a dangerously low white blood cell count, low platelet count, and hair loss. (Supachai *et al.*, 2012; Finberg *et al.*, 2012). Metronidazole is used for giardiasis. The adverse effects associated with systemic metronidazole therapy include: nausea, diarrhoea, weight loss, abdominal pain, vomiting, headache, dizziness and metallic taste in the mouth (Rossi, 2013; Granados *et al.*, 2012; Karamanakos, 2008).

Deedan is available in capsule form (500mg). Deedan has following ingredients shown in the table 1. (CCRU, 2007).

The study was aimed to determine the safety of capsule Deedan in albino Wistar rats. Deedan is prescribed to patients for a period of one month, hence the subchronic oral toxicity (repeated dose-90 day toxicity study) was studied as per schedule Y (Drugs Standard Control Organization, 2005).

**Table 1:** Ingredients of Capsule Deedan.

INGREDIENT	ENGLISH / SCIENTIFIC NAME.	AMOUNT
Maghz-e-karanjwa	Physic Nut, Mulacca Bean/Caesalpinia bonducella	71.5mg
Habbul Neel	Indigo, Pharbitis Nil /Indigofera tinctoria	71.5mg
Tukhm-e-Hanzal	Colocynth / Citrullus colocynthis	71.5mg
Turbud	Turpeth / Operculina turpethum	71.5mg
Kamila	Indian Kamila / Mallotus philippensis	71.5mg
Palaspapra	Bengal Kino Tree, Flame of the forest / <i>Butea monosperma</i>	71.5mg
Afsanteen	Worm Wood, Southern Wood / <i>Artemisia absinthium</i>	71.5mg
<b>Total</b>		<b>500mg.</b>

## MATERIAL AND METHODS

### Experimental Animals

The experimental animals (young, healthy Albino rats of Wistar Strain) were procured from IIIM, Jammu. These rats were kept in the animal house and were observed during the quarantine and acclimatization period. A veterinary examination was conducted 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 at a temperature of 20 – 25°C with 12:12 hour dark and light cycle. The rats were provided pelleted feed procured from Pranov Agro Industries, New Delhi and filtered/sterilized water (Aqua Guard KENT RO).

### Test Item

Deedan capsules were procured from the Central Research Institute, Hyderabad, India. (batch No U269, manufacture May 2011). They were encapsulated and powder was weighed according to the calculations based on body weight of rats. The powder was mixed with water and a suspension was prepared.

### Subchronic oral toxicity

The Subchronic oral toxicity was conducted in accordance to the OECD Guideline 408 (OECD, 1998). The rats were randomly divided into 4 groups each group consisted of 5

rats. The Group I and II being the male and female Controls were orally treated with water (Vehicle). The Group III and IV being the drug treated male and female rats, were orally administered with Deedan at the dose of 300 mg/kg body weight for 90 days daily. All the animals were closely examined for any adverse toxic signs, behavioural changes etc. The body weight of the rats was recorded weekly. Food and Water consumption / rat / 24 hours were recorded weekly. On the 91<sup>th</sup> day, after over-night fasting, all the animals were sacrificed by exsanguination 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 Biochemistry parameters. All the animals were dissected to check macroscopic morphology of the body organs/tissues. The organs such as liver, lung, kidney, spleen, brain, ovary/testes and heart were collected to determine the organ weight followed by grossing for the collection of tissues for Histopathological studies.

### Biochemistry Parameters

Biochemical parameters were studied in serum obtained after centrifugation of blood at 2000 RPM for 15 minutes on the day of the rat sacrifice. Biochemical parameters were determined on fully automatic biochemistry analyzer (XL600 TRANSASIA) using ERBA kits. Liver function tests- aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), Total bilirubin, total protein and albumin and kidney function tests- blood urea, uric acid and other biochemical substances such as glucose, Cholesterol and Triglycerides were estimated.

### Haematological Parameters

Haematological parameters were analyzed in freshly collected blood in blue tap vacutainer containing EDTA anticoagulant. The blood was gently mixed with the EDTA anticoagulant coated on the tube walls. Haematological parameters were determined on 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.

### Histopathology

Tissue samples were collected from the organs of control as well as experimental male / female rats of the subchronic study. The tissue collected from the organs such as liver, lung, kidney, spleen, brain, ovary/testes and heart were 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 were carried on Automatic tissue processor Model No1020 (LIECA make Germany). The tissue processing included dehydration in graded isopropyl alcohol, clearing in xylene I & II, impregnation in paraffin wax and finally tissue blocks was prepared on paraffin block making Model No1150H+C (LIECA make Germany). Section cutting of tissue blocks was done using microtome (YORCO) to the thickness of 5 – 8 microns. The tissue sections were fixed on the slide by heat technique following by the staining by Haematoxylin and Eosin stain. The staining was carried on Automatic slide stainer (THERMO MAKE Germany) haematoxylin and eosin staining. After staining the tissue section were mounted with DPX to prevent any damage to the stained tissue. The stained tissue sections were examined under microscope 40X objective to check the adverse effects of drug on cell morphology as well as on the cell organelles.

### Statistical analysis

All results are expressed as mean  $\pm$  standard deviation. Comparison of all results on body weight, food & water consumption, haematological value, biochemical values, were performed using one way analysis of variance (ANOVA) method using statistical software SPSS version 16.0. Probability of 0.05 or small ( $p \leq 0.05$ ) was used as the criterion of significance.

## RESULTS

### Effect of Deedan on body weight and growth

The male and female deedan treated rats grew up in a normal fashion and gained body weight with the similar rate as those of respective control males and females. The percentage gain in body weight is shown in the table 2.

**Table 2:** Percentage gain in body weight of treated and control groups.

Group	% gain in body weight
Male (Treated)	124.82
Male (Control)	122.22
Female (Treated)	78.50
Female (Control)	73.84

The values are expressed as mean  $\pm$  SEM. n=5 in each group. \* $p < 0.05$  as compared with the controls at the same time (one-way ANOVA)

### Effect of Deedan on Mean Food and Water consumption

There was no significant change in the feed and water consumption of Deedan treated male and female rats when compared with the respective control males and females as shown in table 3.

**Table 3.** Feed and water consumption of treated and control groups.

	Mean Food consumption per rat/24 hours. (Grams)		Mean Water Consumption per rat/24 hours. (Millilitre)	
	Male	Female	Male	Female
Control	17.6 $\pm$ 1.5	18.0 $\pm$ 1.87	30.64 $\pm$ 1.4	29.1 $\pm$ 1.7
Treated	17.1 $\pm$ 1.1	17.2 $\pm$ 0.83	31.2 $\pm$ 1.8	29.4 $\pm$ 1.2

The values are expressed as mean  $\pm$  SEM. n=5 in each group. \* $p < 0.05$  as compared with the controls at the same time (one-way ANOVA)

### Biochemistry Parameters

The rats administered with Deedan daily for 90 days were found to have normal organ function tests (e.g. Kidney function test and liver function test). The lipid profile of the drug treated rats were also found to be insignificantly changed by the Deedan administration except triglyceride levels were found to be reduced in both male and female Deedan treated rats. There was also insignificant change in other metabolic tests e.g. glucose when compared with the respective controls. Table 4 shows the biochemical parameters of Deedan treated rats and control rats.

**Table 4:** Biochemical parameters of Deedan treated rats and control rats.

Parameter	Male		Female	
	Control	Treated	Control	Treated
<b>Liver function tests</b>				
ALT (IU/L)	92 $\pm$ 9.12	98.56 $\pm$ 11.2	95.5 $\pm$ 8.4	88.3 $\pm$ 14.2
AST (IU/L)	137 $\pm$ 14.9	142 $\pm$ 15.7	136 $\pm$ 20.4	129 $\pm$ 19.6
ALP (IU/L)	166.5 $\pm$ 30.4	161.8 $\pm$ 39.2	149.7 $\pm$ 26.3	151.6 $\pm$ 28.8
TOTAL BILIRUBIN(mg/dl)	0.18 $\pm$ 0.06	0.22 $\pm$ 0.04	0.21 $\pm$ 0.04	0.25 $\pm$ 0.05
TOTAL PROTEIN (g/dl)	7.66 $\pm$ 0.26	7.61 $\pm$ 0.27	8.42 $\pm$ 0.23	8.18 $\pm$ 0.16
ALBUMIN (G/dl)	4.16 $\pm$ 0.07	4.14 $\pm$ 0.19	4.56 $\pm$ 0.21	4.68 $\pm$ 0.34
<b>Kidney function tests</b>				
UREA (mg/dl)	40.85 $\pm$ 4.4	46.58 $\pm$ 5.6	50.6 $\pm$ 8.5	47.8 $\pm$ 8.4
URIC ACID (mg/dl)	3.15 $\pm$ 0.72	2.89 $\pm$ 0.82	2.49 $\pm$ 0.85	2.90 $\pm$ 0.91
<b>Metabolic function tests</b>				
GLUCOSE (mg/dl)	91 $\pm$ 9.9	97 $\pm$ 12.3	88.9 $\pm$ 8.7	92.6 $\pm$ 10.2
CHOLESTROL (mg/dl)	53.3 $\pm$ 7.6	56.1 $\pm$ 7.6	52.8 $\pm$ 8.9	58.2 $\pm$ 10.2
TRIGLYCERIDE (mg/dl)	95.1 $\pm$ 9.4	57.2* $\pm$ 10.1	85.4 $\pm$ 12.7	49.9* $\pm$ 7.7

The values are expressed as mean  $\pm$  SEM. n=5 in each group. \* $p < 0.05$  as compared with the controls at the same time (one-way ANOVA)

### Haematology Parameters

The hematological parameters of the both male and female Deedan treated rats were found to be insignificantly unchanged when compared with the respective controls as shown in Table 5.

**Table 5:** Hematological parameters of Deedan treated rats and control rats.

Parameter	Male		Female	
	Control	Treated	Control	Treated
WBC ( $10^3/\mu$ l)	14.54 $\pm$ 3.18	12.26 $\pm$ 7.66	14.12 $\pm$ 4.52	13.47 $\pm$ 6.91
RBC ( $10^6/\mu$ l)	10.44 $\pm$ 0.58	9.83 $\pm$ 0.38	8.59 $\pm$ 0.84	8.49 $\pm$ 0.50
Haemoglobin (g %)	17.3 $\pm$ 0.42	16.7 $\pm$ 0.64	15.56 $\pm$ 0.55	16.04 $\pm$ 0.87
HCT (%)	51.1 $\pm$ 1.8	50.7 $\pm$ 1.92	45.66 $\pm$ 3.30	48.02 $\pm$ 2.85
MCV (Femto liter)	48.9 $\pm$ 4.5	51.8 $\pm$ 3.88	53.16 $\pm$ 4.4	56.62 $\pm$ 6.23
MCH (Pico grams)	16.6 $\pm$ 0.28	17.06 $\pm$ 0.40	15.1 $\pm$ 0.86	17.02 $\pm$ 0.56
MCHC (g %)	33.85 $\pm$ 0.35	32.94 $\pm$ 0.44	34.1 $\pm$ 0.86	33.46 $\pm$ 0.72
Reticulocyte (%)	3.19 $\pm$ 0.32	3.44 $\pm$ 0.32	3.13 $\pm$ 0.26	2.92 $\pm$ 0.31
Platelet ( $10^3/\mu$ l)	1327 $\pm$ 171	1326 $\pm$ 142	1278 $\pm$ 137	1331 $\pm$ 151

### Differential Leucocyte Count

Neutrophil (%)	11.9 $\pm$ 1.22	9.98 $\pm$ 1.26	7.4 $\pm$ 1.82	8.65 $\pm$ 1.45
Lymphocytes (%)	71.1 $\pm$ 5.25	80.64 $\pm$ 6.11	74.86 $\pm$ 3.88	84.66 $\pm$ 6.29
Monocyte (%)	9.99 $\pm$ 0.82	7.46 $\pm$ 0.7	7.82 $\pm$ 0.63	6.52 $\pm$ 0.92
Eosinophil (%)	0.71 $\pm$ 0.1	0.81 $\pm$ 0.04	0.73 $\pm$ 0.05	0.66 $\pm$ 0.02
Basophiles (%)	0.24 $\pm$ 0.08	0.26 $\pm$ 0.05	0.27 $\pm$ 0.10	0.29 $\pm$ 0.04

The values are expressed as mean  $\pm$  SEM. n=5 in each group. \* $p < 0.05$  as compared with the controls at the same time (one-way ANOVA)

### Histopathological results

The tissue slides of various organs/tissues collected from the Deedan treated males and females were found to be normal in

shape, size and texture when compared with the respective control tissue slides. Fig.1 to Fig. 7. Shows different slides of deedan treated and control tissues, as observable there is no major difference in treated and control slides.

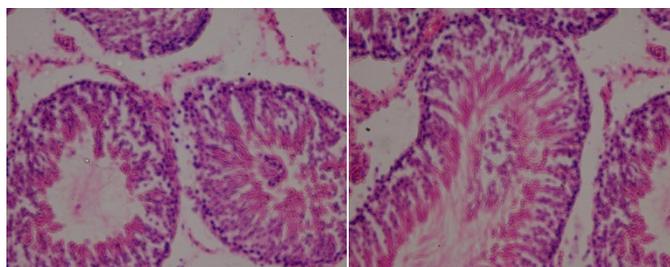


Fig. 1a: Treated Testes

Fig. 1b: Control Testes

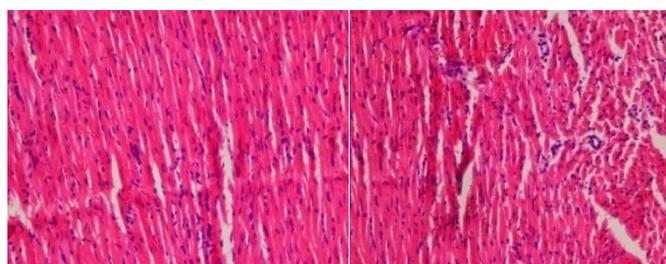


Fig. 2a: Treated Heart

Fig. 2b: Control Heart

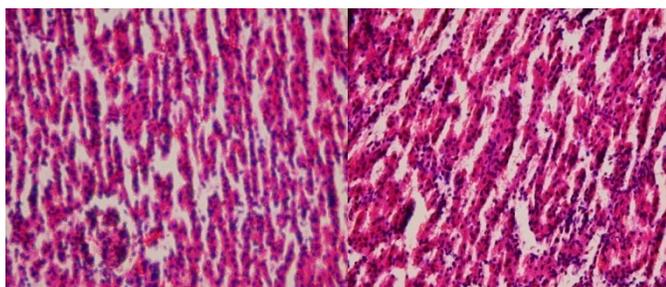


Fig. 3a: Treated Lungs

Fig. 3b: Control Lungs

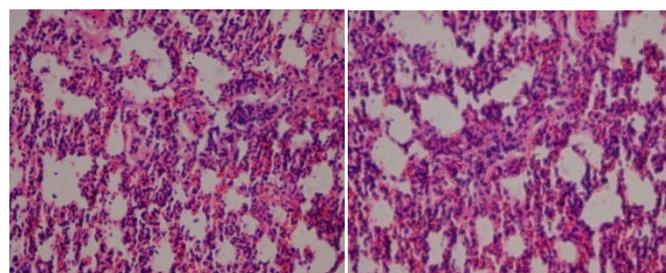


Fig. 4a: Treated Lung

Fig. 4b: Control Lung

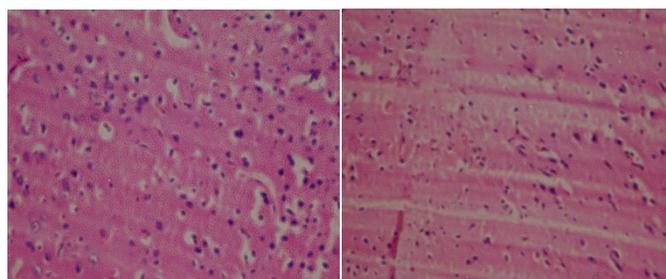


Fig. 5a: Treated Brain

Fig. 5b: Control Brain

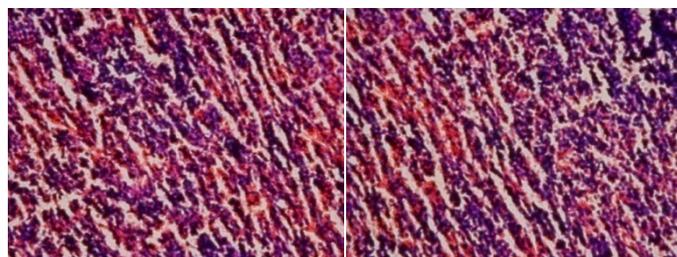


Fig. 6a: Treated Spleen

Fig. 6b: Control Spleen

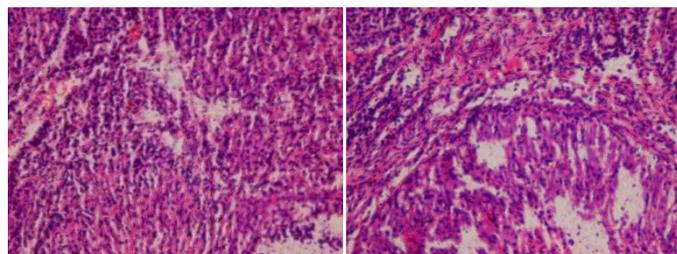


Fig. 7a: Treated Ovary

Fig. 7b: Control Ovary

## DISCUSSION

Experimental screening method is imperative in order to establish the safety and efficacy of traditional and herbal products and also to set up the active components of the herbal products (Mythilypriya *et al.*, 2007). Unani system of medicines and herbal products have ever been used for their efficacy and low costs, however their safety is yet to be evaluated on scientific guidelines (Riaz *et al.*, 2010; Barnes *et al.*, 2004). Herbs and Unani system of medicines can be toxic and have adverse effects in patients, when used for inappropriate indications, or prepared inadequately or used in large excessive doses for prolonged durations (Fong, 2002; Phua *et al.* 2009; Chan *et al.* 2003).

Keeping in view the importance of safety evaluation of Unani system of medicines, the current study was aimed to evaluate its safety profile in rats. Deedan in capsule form is given to patients having concentration of 500mg. When calculated the human dose was found to be 14.4 mg/kg/day, equivalently the extrapolated rat dose was found to be 100mg/kg/day. The dose level selected for the subchronic toxicity (300mg/kg/day) was three fold the extrapolated rat dose.

There was no mortality or any abnormal behaviour found in the rats treated with Deedan for 90 days at the dose level of 300mg/Kg of body weight depicting its unlethal action. The rats grew up normally and their body weight gains were found to be in concordance with the controls. The food habit and water consumption of drug treated rats were found to be unaffected by the Deedan administration. There was no significant change in the biochemical parameters of the Deedan treated male and female rats when compared with the controls except the triglyceride levels was found to be reduced. . The decrease in serum Triglyceride by Deedan in both sexes of rats is possibly due to the effects of Tukhm-e-Hanzal (*Citrullus colocynthis*) and Turbud (*Operculina turpethum*) as the plant materials of these two herbs have been reported to be hypolipidemic (Rahbar *et al.* 2010; Sharma *et al.*,

2012). Various hematological parameters of male and female treated rats were also found to be unaffected by the Deedan administration. The histopathological study of Deedan treated male and female revealed nontoxic effect of Deedan as there was no abnormality (shape, size, number and texture) observed in any tissue slide of the Deedan treated male and female rats.

## CONCLUSION

The Unani polyherbal formulation – Deedan when administered to the rats daily for 90 days at the dose level of 300 mg/Kg of body weight was found to be safe under these circumstances.

## CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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