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ACUTE ORAL TOXICITY AND EFFICACY OF URICARE TABLET (POLYHERBAL FORMULATION) AGAINST BPH (BENIGN PROSTATIC HYPERPLACIA)

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ABSTRACT

Aim: To evaluate acute oral toxicity of Uricare Tablet (Anti BPH Herbo-mineral formulation) on Swiss albino mice and its efficacy against Benign Prostatic Hyperplasia (BPH). **Method:** This study was conducted according to OECD guideline AOT-425. The IAEC no. for the study is SKPCPER/IAEC/2016-02/03. The extract was administered orally at a single oral dose of 2000 mg/kg of in sequence at 48 h intervals. The mice were observed continuously for behavioral changes, autonomic profiles and other signs of toxicity or mortality up to a period of 14 days. The body weight, food intake and water intake were also observed on 1st, 7th and 14th day. The effect of test drug was assessed on Testoviron Depot (TD) injection (2.5mg /kg /day) induced BPH in male wistar rats. The body weight, urine volume, kidney markers and physical parameters of prostate were analyzed by following provided methods at the end of study. **Results:** There were no physical and behavioral changes observed in Swiss albino mice during 14 days. Body weight of all animals did not reveal any significant change as compared to vehicle control group. Mortality was not observed in any animal of a group. Uricare Tablet showed significant effect on body weight, urine volume and different prostatic and biochemical parameters. All the parameters were normalized in test drug treated group. **Conclusion:** The study shows that Uricare Tablet (Anti BPH Herbo-

Mineral formulation) does not produce any toxic effect at dose of 2000 mg/kg and normal value of kidney markers and physical prostate parameter suggests its effectiveness against BPH.

KEYWORDS: Anti BPH Poly herbal formulation, Uricare tablet, NOAEL, Mortality, OECD Guideline.

INTRODUCTION

Herbal medicines are popular remedies for diseases used by a vast majority of the world population.[1] Mostly among them are poly herbal formulations (BPH) which are prepared in a number of dosage forms.[2] They enhance the therapeutic action and reduce the concentrations of single herbs hence poly-herbal formulations are utilized by the mankind.[3] Uricare tablet is a one of Herbo-mineral formulation indicated for urinary track problems, burning urination, renal calculi, acute and chronic renal failure and Prostatitis.

Despite the widespread use, there is a lack of scientific evidence on their efficacy and safety.[4] Hence it is necessary to evaluate formulations by modern scientific methods in order to demonstrate their toxic effects to prevent harm.[5] Acute oral toxicity study is characteristic of the test which has to be confirmed before human trails that is in preclinical phase to discover potential toxic effects of drugs if any.

With the above considerations, the present study was aimed to assess the acute oral toxicity of novel Anti BPH poly herbal formulation and to establish its efficacy in BPH.

AIM AND OBJECTIVES

- To evaluate acute oral toxicity of Uricare tablet (Anti BPH Herbo-mineral formulation) on Swiss albino mice.
- To evaluate efficacy of Uricare tablet (Anti BPH Herbo-mineral formulation) Induced by testoviron depot injection in male wistar rats.

MATERIALS AND METHODS

Material: The test drug Uricare tablet was manufactured at Petlad Mahal Arogya Mandal Pharmacy, At. & post. Pipalata, Dist. Kheda, Gujarat, India. All the GMP standards were followed during manufacturing. The detail of Uricare Tablet is mentioned below;

Table 01: Ingredients of Uricare Tablet.

Sl. No.	Name of Ingredient	Quantity
1	Ext. *Crataeva religiosa*	80 mg
2	Ext. *Boerhavia diffusa*	80 mg
3	Ext. *Tinospora cordifolia*	80 mg
4	*Commiphora mukul*	80 mg
5	*Shuddha Shilajit*	80 mg

Method: This study was conducted according to OECD guideline AOT-425 at Shree S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Ganpat Vidyanagar-384012, Gujarat, India. The detail of study is mentioned below;

(A) Acute oral toxicity[12]: It was conducted according to OECD guideline AOT-425 to know single dose toxicity of test drug on swiss albino mice. All the animals were acclimatized and kept in proper cages with proper diet. A limit dose of extract (2000 mg/kg) was used in each mouse in sequence at 48 h intervals. Animals were observed individually at least once during the first 30 min after dosing, periodically during the first 24h, and daily thereafter, for a total of 14 days for any clinical signs of toxicity or mortality. Body weight of all animals was recorded once in a week. The detail of dosing record is as follow;

Table 02: Individual animal dosing record.

Expt. Day	Animal No.	Gender	Test substance (mg or ml)	Vehicle Distilled Water (ml)	Volume dosed (ml)	Conc. (mg/ml)
1st day	H	M	55	0.6	0.55	91.67
3rd day	B	M	60	0.6	0.54	100
5th day	T	M	60	0.6	0.56	100
7th day	HT	M	60	0.6	0.58	100
9th day	UM	M	55	0.6	0.57	91.67

Expt.: Experiment, Conc: Concentration, H: Head, B: Body, T: Tail, HT: Head & Tail, UM: Unmarked, M: Male, F: Female

(B) Effect on BPH: This study was performed in Testoviron depot injection induced BPH in male wistar rats. Animals assigned for study were randomized in four groups (6 animals in each) and maintained in standard condition in accordance with the guideline of the CPCSEA.

Table 03: Animals Grouping for Uricare Tablet study.

Group No.	Group Name	Dose	No. of animals
I	Vehicle control group (NC)	Olive oil- 1mg/kg/day	6
II	Disease control group (DC)	Injection Testoviron depot 2.5mg/kg/day	6
III	Standard drug treated group (Std.)	Finasteride 1mg/kg/day	6
IV	Uricare tablet (UT)	200mg/kg/day	6

Testoviron depot injection [Testosterone propionate(25 mg/kg) + Testosterone enanthate (250 mg/kg) - Zydus pharma] was given 2.5mg /kg /day through S.C. route in healthy male wistar rats of group II, III and IV for consecutive 21 days to induce BPH. Group III was administered with standard drug [Tab. Finasteride (1mg/kg/day) - Cipla pharma] orally for 21 days. Uricare Tablet (200mg/kg/day) was given orally in group IV for 21 days.

At the end of study, Urine volume was measured by keeping them individually in metabolic cages for 6 h. The animals were anesthetized by diethyl ether and blood sample was collected by retro-orbital route for evaluation of kidney markers (parameter analyzer kit - Euro diagnostic systems PVT.LTD.) and Serum dihydro-testosterone (DHT) level (at Supratech Micropath laboratory, Himatnagar). After that rats were euthanized by cervical dislocation and the prostate gland was isolated for the measurement of physical parameters i.e. size, weight, length, width and index.

OBSERVATIONS AND RESULT

(A) Acute oral toxicity: The animals were observed continuously for behavioural changes, autonomic profiles and other signs of toxicity or mortality up to a period of 14 days. The body weight, food intake and water intake were also observed on 1st, 7th and 14th day. There were no physical and behavioural changes observed in Swiss albino mice during 14 days. Body weight of all animals did not reveal any significant change as compared to vehicle control group. Mortality was not observed in any animal of a group.

Table 04: Showing individual animal weekly body weight record, dose & Mortality record.

Animal No.	Sex	Given Dose (mg/kg)	Experiment Day & Date Unit : gm			Mortality
			1st	7th	14th	
H	M	2000	25	26	27	NIL
B	M	2000	27	28	29	NIL
T	M	2000	28	28	29	NIL
HT	M	2000	29	30	31	NIL
UM	M	2000	26	27	28	NIL

H: Head, B: Body, T: Tail, HT: Head & Tail, UM: Unmarked, M: Male, F: Female

(B) Effect on BPH: The effect of test drug on various physical, serum parameters and prostate are as follow;

Urine volume of test drug treated animals was found increased as compared to DC group.

Body weight of test drug treated animals was found to be normalized compared to DC group.

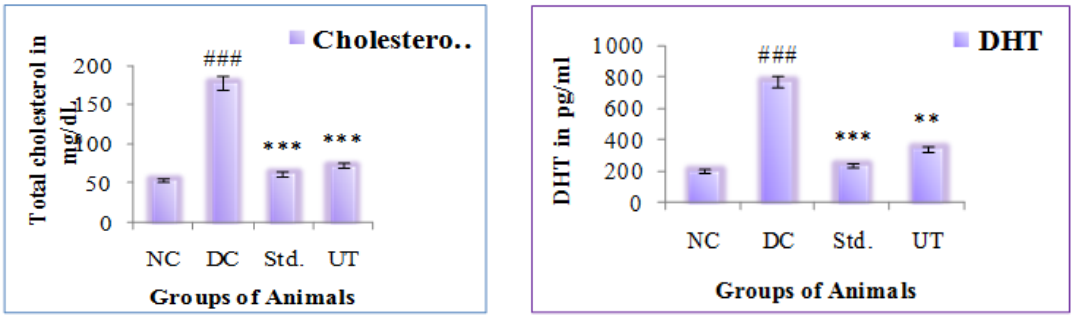
Table 05: Details of effect on body weight (gm).

Group	1st week	2nd week	3rd week	4th week
I (NC)	125	196	211	239
II (DC)	124	197	216	254
III (Std)	124	188	201	230
IV (UT)	124	172	191	221

Table 06: Details of effect on serum parameters.

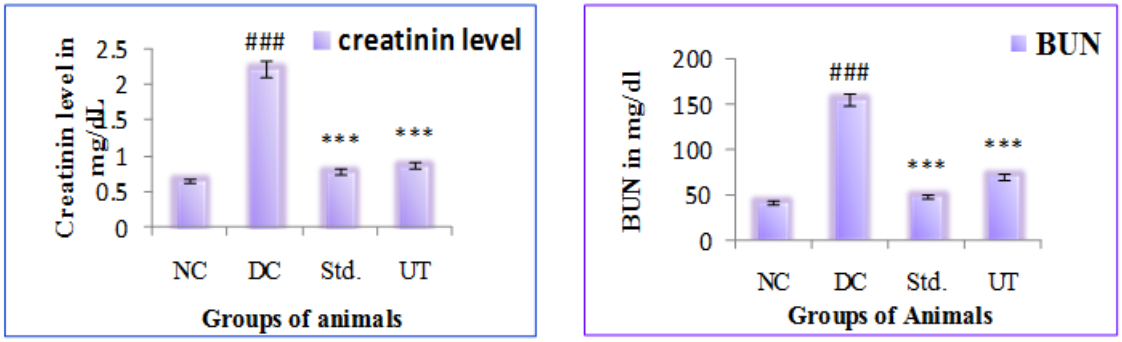
Group	Cholesterol level	Creatinin level	BUN	Total protein	Albumin level	Globulin level	A/G ratio	DHT level
I (NC)	54.67	0.656	42.19	5.36	3.37	1.987	1.81	205
II (DC)	178.3	2.217	156.1	12.94	6.03	6.91	0.98	775
III (Std)	63	0.783	48.09	6.56	3.97	2.597	1.74	235
IV (UT)	72.67	0.873	54.58	8.5	4.28	4.218	1.013	342.5

BUN: Blood Urea Nitrogen, DHT: Dihydro-testosterone



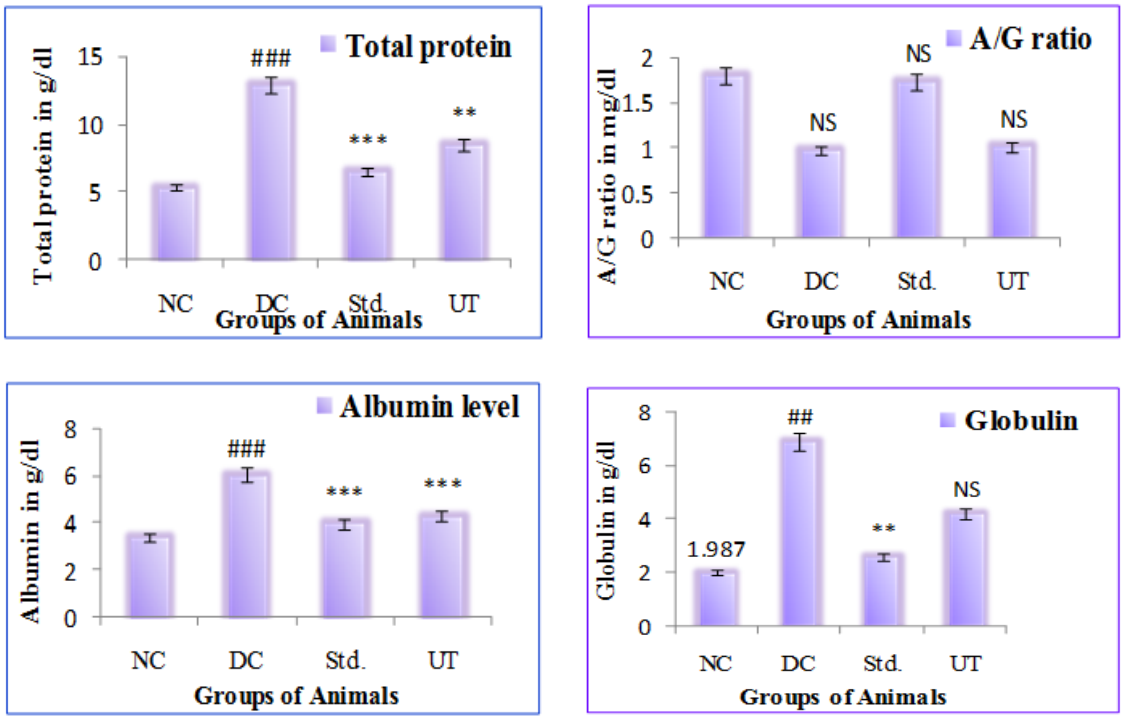
Graph 2: Cholesterol, DHT level (Values are expressed as mean ± S.E.M., n=6).

###p < 0.001 Vs Normal control, ***p < 0.001 Vs Disease control, **P < 0.01 Vs Disease control group



Graph 3: Creatinin, BUN level (Values are expressed as mean ± S.E.M., n=6).

###p < 0.001 Vs Normal control, ***p < 0.001 Vs Disease control.

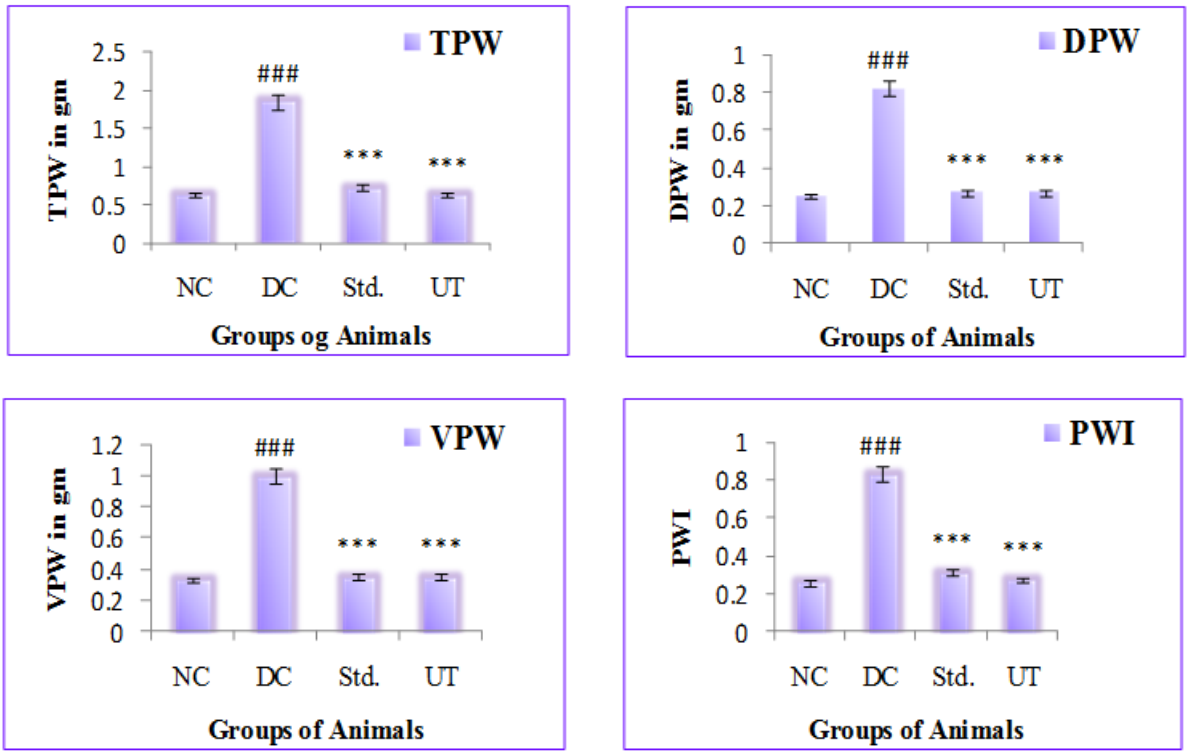


Graph 4: Total protein, Albumin level, Globulin level, A/G ratio (Values are expressed as mean ± S.E.M., n=6).

###p < 0.001 Vs Normal control, ***p < 0.001 Vs Disease control, **P < 0.01 Vs Disease control group, NS: Non significant

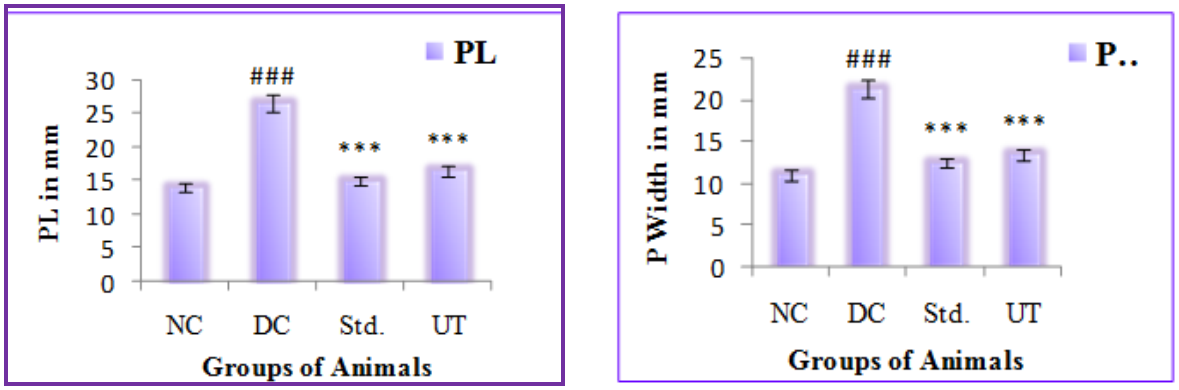
Table 07: Details of effect on Prostatic parameters.

Group	TPW	DPW	VPW	PL	PW	PWI
I (NC)	0.621	0.2564	0.3371	14	11	0.257
II (DC)	1.844	0.8242	0.9966	26.5	21.5	0.832
III (Std)	0.72	0.2721	0.3543	15	12.5	0.312
IV (UT)	0.618	0.2716	0.3539	16.5	13.5	0.272



Graph 5: TPW, DPW, VPW, PWI (Values are expressed as mean ± S.E.M., n=6).

###p < 0.001 Vs Normal control, ***p < 0.001 Vs Disease control.



Graph 6: PL, PW (Values are expressed as mean ± S.E.M., n=6).

###p < 0.001 Vs Normal control, ***p < 0.001 Vs Disease control.

DISCUSSION

Herbal medicine is the oldest form of health care and has been used by all the traditions throughout several decades. The WHO has assessed that 80% of world population prefers using traditional therapy as a main part of health care tool.[7]

The safety of herbal medicines use has recently been questioned due to reports of illness and fatalities. All though there are many traditional herbal medicines available, only a few have been verified by clinical trials.[8] (Patrick).

Generally, above 50 year old male have BPH disorder because of the hormonal imbalancein stromal and epithelial tissue of the prostate gland. Testosterone hormone level aremainly important to producing the BPH, because testosterone are converted into DHT by5α-reductase enzyme and stimulate the stromal tissue and increase the cell division inprostate gland it can obstruct the urination. After producing BPH, physically andbiochemical changes in body like increase the prostate weight, size, length, width. Biochemically, increase the DHT level, Creatinine level, Cholesterol Level, BUN, Totalprotein, Albumin level, and Globulin level.

Uricare Tablet is Herbo-Mineral Formulation having Anti BPH effect. *Crataevareligiosa* improves the urinary flow rate as reducing post-void residual urine.[9] *Borehavia diffusa* have anti inflammatory and anti poliperative effect which helps in reducing size of prostate.[10] Treatment with gugulipid of *Commiphora Mukul* significantly inhibit the viability of human prostate cancer cell line.[11] The alcoholic extract of *T.cordifolia* have anti-inflammatory actions in models of acute and sub-acute inflammation.[12] *Shilajita* is a very famous herbo mineral substance found in the Indian Himalayan region. It is used for treating the inconvenience in urination because of the enlarged prostate gland in BPH.[13] These durgs helps in several conditions occurring in BPH like frequent urination, UTI, loss of bladder control etc.

In the present study Uricare Tablet Herbo-Mineral Formulation was studied for its acute toxicity. No remarkable changes were observed in animal behaviour, mortality rate was observed zero. There was remarkable increase in body weight of swiss albino mice, which proves efficacy and safety of the current poly-herbal formulation. Urine volume of test drug treated animals was found increased as compared to DC group. Body weight of test drug treated animals was found to be normalized compared to DC group.

The effect of test drug against BPH was performed in testoviron depot injection induced BPH in male wistar rats. The body weight of test drug treated group was found normal as compared to DC group (Table 5). The urine volume was observed restored and increased in drug treated group as compared to DC group may be due to its diuretic and anti inflammatory properties. UT brought DHT level nearby normal (Table 6) which indicates its 5α-reductase enzyme inhibitory property. The significant decrease was found in kidney markers i.e. cholesterol, BUN, Creatinin, total protein, albumin, globulin, A/G ratio (Table 6) and

Prostatic parameters i.e. weight, size, length, width, index (Table 7) in test drug treated group as compared to DC group which proves its potential effect in BPH.

CONCLUSION

Toxicity study was performed according to OECD 425 guideline. Uricare Tablet(Polyherbal formulation)found safe up to the dose of 2000 mg/kg. Biochemical parameters (Total cholesterol, total protein, BUN, Creatinin, DHT level), physical parameters (TPW, DPW, VPW, PL, PWI, and P.Width) found nearer to normal range in Uricare Tablet (polyherbal formulation) treated group. So it suggests Uricare Tablet (polyherbal formulation) possess effectiveness against BPH and it might be inhibit the 5α-reductase enzyme and found normalise valueof DHT in BPH.

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1. Petlad Mahal Arogya Mandal Pharmacy, At.& Po. Pipalata, Dist. Kheda, Gujarat, India.
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