Research Article

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<ABS_TL>**ABSTRACT**

<ABS>PijusaballiRasa (PJB) is an Ayurvedic preparation ~~which is~~ used as a traditional medicine in the treatment of edema in the rural population. The acute pharmacological test of PJB recorded no death or any signs of toxicity even at the highest dose of 4000 mg/~~Kg~~ kg body weight. To find out the effect of chronic administration of PJB on serum chemistry profile, it was administered chronically to the male Sprague-Dawley rats at a dose of 400 mg/kg. After 28 days of chronic administration of the PJB preparation, the serum chemistry profile, composed of a battery of tests, allowed for evaluation of several body systems and assessment of metabolic disturbances. The results of the effect of chronic administration of PJB on serum chemistry profilewere as follows.~~the effect on serum chemistry profile after chronic administration are thus:~~There ~~is~~ wasa statistically highly significant (p=0.003) decrease in the total protein in the serum of the male rat~~s~~{(9.45% decrease~~)~~.). There ~~is~~ wasa statistically highly significant (p=0.010) increase in the albumin level in the serum of the male rat~~s~~{(24.66% increase~~)~~.). There ~~is~~ wasa statistically very highly significant (p=0.001) decrease in the globulin level in the serum of the male rat~~s~~{(45.50% decrease~~)~~.). There ~~is~~ wasa statistically significant (p=0.015) increase in the albumin~~.~~/globulin ratio in the serum of the male rat~~s~~{(175.19% increase~~)~~.).There ~~is~~ wasa statistically significant (p=0.014) increase in the uric acid level in the serum of the male rat~~s~~{(25.16 % increase~~)~~.).

<KWD>**Keywords:**Pijusaballi Rasa~~,~~; ~~Oe~~Edema~~,~~; Ayurvedic~~,~~; Albumin~~,~~; Globulin~~,~~; Uric ~~acid~~Acid~~.~~

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<H1>INTRODUCTION

Ayurvedic medicines have a reputation as decent and effective remedies for a number of diseases [1]. Currently, the World Health Organization (WHO) has officially recognized and recommended large-scale use of herbal (Unani and Ayurvedic) medicines, particularly in the developing countries, as an alternative system of medicine to deliver health-care services at the primary health-care level [2]. According to WHO, approximately 1.5 billion people ~~of~~ aroundthe world are now getting ~~treatment~~ treatedwith these medicines [3]. They also have a good safety profile ~~also~~ [4].

Pijusaballi Rasa (PJB) is an Ayurvedic preparation ~~which is~~ used as a traditional medicine in the treatment of edema in the rural population [5-11].

~~Pijusaballi Rasa~~PJB~~is~~ has beenincluded (pages 246-247) in the
1992 (~~Approved~~ approved by the Government of

1991) [5].

The use of herbal preparations without any standard dosage along with inadequate scientific studies on their safety profile has raised concerns on their toxicity [12]. That is why~~,~~ we ~~designed our current experiment~~developed this study to observe the effect of chronic administration of PJB to Sprague-Dawley rats at a high dose. The objective is to have a better understanding of the potential toxicological profile of the drug and to decide how justifiable the use of this drug is under the stated conditions. The study provides directions for further research as well.

<H1>MATERIALS AND METHODS

<H2>Drugs, ~~Chemicals~~chemicals, and ~~Reagents~~reagents~~:~~

For this research work to characterize the Kidney function profile, ~~Pijusaballi rasa (~~PJB~~)~~ was collected from Sri .Ketamine injection was purchased from , Limited, . All other reagents, assay kits, and chemicals used in this work were purchased from Human GmbH, Wiesbaden, Germany.

<H2>Experimental ~~Animals~~animals~~:~~

Six-to-eight-week~~s~~-old male Sprague-Dawley rats bred and maintained at the animal house of the Department of Pharmacy, University, were used in this hematological experiment. These animals were apparently healthy and each weighed 50-70g. The animals were housed in a well-ventilated clean experimental animal house under constant environmental and adequate nutritional conditions throughout the period of the experiment. They were fed with rat chow prepared according to the formula developed at of Scientific and Industrial Research~~-~~ . Water was provided ad libitum and the animals were maintained at 12 hours day and 12 hours night cycle. All experiments on the rats were carried out in absolute compliance with the ethical guide for care and use of laboratory animals approved by Ethical Review Committee, Faculty of Life Sciences, Department of Pharmacy, University.

<H2>Experimental ~~D~~design

<H3>**Acute ~~Toxicity toxicity Studystudy~~:**The acute oral pharmacological test was performed ~~following as per~~the guidelines of Organization for Economic Co-operation and Development (OECD) for testing of chemicals with minor modifications (OECD Guideline 425) [13]. Sixteen male ~~mice~~ Sprague-Dawley rats(30-40 g body weight) were divided into four groups,~~of~~ each groupcomprising four animals ~~each~~. Different doses (1000 ~~mg/kg~~, 2000 ~~mg/kg~~, 3000 ~~mg/kg~~, and 4000 mg/kg) of the experimental drug (PJB) were administered to the rats by stomach tube. The dose was divided into two fractions and given within 12 hours. Then all the experimental animals were observed for mortality and clinical signs of toxicity (general behavior, respiratory pattern, cardiovascular signs, motor activities, reflexes, and changes in skin and fur texture) at 1, 2, 3, and 4 hours and thereafter once a day for the next ~~three~~ 3days following PJB administration.

<H3>**Chronic toxicity studies**: Prior to the experiment, rats were randomly divided into ~~2~~ twogroups of ~~8~~ eightanimals each. One group was treated with PJB and another was used as control. The control animals were administered with distilled water only,at a volume same as the drug ~~treated~~ administeredto the study group for 28 days. For all the pharmacological studies, the drugs were administered per oral route at a dose of 400 mg/Kg body weight [14]. After acclimatization, the Ayurvedic medicinal preparation was administered to the rats by intra-gastric syringe between ~~the~~ 10 am ~~to~~ and12 am daily throughout the study period [15-19]. All the experimental animals were marked carefully on the tail, which helped to uniquely identify them ~~particularly~~. ~~By u~~Using identification marks, responses were noted separately for a particular period prior to and after the administration [20].

<H3>**Blood ~~Samples samples Collection collection~~ and ~~Preparation~~ preparation of ~~Serum~~serum:**At the end of the 28 days treatment period,after 18 hours of fasting,rats from each group were an~~a~~esthetized by administration (i.p.) of ketamine (500 mg/kg body weight) ~~after 18 hour fasting~~ [21-~~29~~28]. For biochemical analysis,~~Blood~~ blood samples were collected from post vena cava of rats into plain sample tubes for serum generation ~~for biochemical analysis~~[~~30~~29]. Serum was obtained after allowing blood to coagulate for 30 minutes and ~~centrifuged~~ centrifugingit at 4000 rpm for 10 minutesusing benchtop centrifuge (MSE Minor, ~~England~~UK). The supernatant serum samples

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were collected using dry Pasteur pipette and stored in the refrigerator for further analysis. All analyses were completed within 24 hours of sample collection [31,32].

<H3>**Determination of Biochemical biochemical Parameters:**Biochemical analysis was carried out on serum to assess the state of the liver [33] and kidney [34]. Biochemical studies involved analysis of parameters such as Total total Protein protein [35], Albumin albumin (by Bromocresol Bromocresolgreen method) [36], Creatinine creatinine [37], Blood blood Urea urea Nitrogen nitrogen (BUN) [38], and Uric uric Acid acid [39]. The absorbance values of inall the tests were determined using spectrophotometer (UV-Visible Spectrophotometer Model No. UV-1601 PC.).

<H3>**Statistical Analysis:** SPSS (Statistical Package for Social Science) Statistics 11.5 package (SPSS Inc., Chicago, Ill) was used to carry out independent sample *t*-test to analyze the data. All values are were expressed as mean ± SEM (Standard error of the mean) and p<0.05, p<0.01, and p<0.001 were taken as the level of significance.

<H1>**RESULTS**

<H2>**Acute Pharmacological pharmacological Study:**
The drug (PJB) administered up to a high dose of 4000 mg/kg produced no mortality. Thus the LD50 (Median median Lethal lethal Dose dose) value was found to be greater than 4000 mg/Kg kg body weight. The animals did not manifest any sign of restlessness, respiratory distress, general irritation, or convulsion. Since PJB is has been in the clinical use for treatment of diseases for many years, a limit test was performed in acute oral toxicity study. According to the OECD test guideline 425, when there is information in support of low toxicity or non-toxicity and low or no immortality nature of the test material, then the limit test at the highest starting dose level (4000 mg/Kg kg body weight) was conducted. There were no signs of mortality and toxicity signs observed at 4000 mg/Kg kg body weight. Therefore, it can be concluded that PJB when administered at single dose is non-toxic and can be used safely in oral formulations.

<H2>**Effect of Pijusaballi Rasa (PJB) on Total total Serum serum Proteinprotein, Albuminalbumin, Globulin globulin content, and Aalbumin/G globulinratio in Male male Ratsrats:**
After 28 days of chronic administration of the Pijusaballi Rasa (PJB) preparation, the total protein, albumin content, and the calculated ratio of albumin to globulins, termed the albumin/globulin (A/G) ratio, in serum were determined in the male rats group. In the study, the total protein content in the serum was decreased (9.45%) in the PJB-treated male rats. The decrease in total protein was statistically highly significant (p=0.003).On the contrary, the albumin content was found to be increased (24.66%) in PJB-treated male rats, and it was statistically highly significant (p=0.010), and there was ahighly significant (p=0.001) decrease(45.50% decr.) in globulin content. As a result the increase (175.19 %) in the Albumin /Globulin ratio from their corresponding control values was statisticallysignificant(p=0.015) (Table 2).

<H2>**Effect of PJB on Creatininecreatinine, BUN, Ureaurea, and Uric uric Acid acid level in male rats:**
The creatinine and blood urea nitrogen(BUN) content in the serum were measured to carry out kidney function test. The levelsseof these two contents compoundscan provide information about how effective the kidney function is. There was a statistically insignificant increase in the creatinine (7.58% incr; p=0.205) content in serum in the PJB-treated male rats and also statistically insignificant (p=0.200) increase of blood urea nitrogen (BUN) level (11.23% incr, p=0.200) in the serum was noted in comparison to their control group. The increase in BUN/ Creatinine creatinine ratio (3.49 % incr) was also statistically insignificant (p=0.702). It was observed that there was a statistically significant (p=0.014) increase (25.16%) in serum uric acid content of PJB-treated male rats in comparison to their control male rats (Table 3).

<H1>**DISCUSSION**

The formulation of Pijusaballi Rasa (PJB) is included composed ofSutaka (suddhaparada), Gandhaka (suddha), Abhra (abhrakabhasma), Tara (rajatabhasma), Lauha (bhasma), Tangana (suddhatankana), Rasanjana (daruharidra), Maksika (bhasma),Lavanga, Candana (svetacandana), Musta (musta), Patha, Jiraka (Svetajiraka), Dhanyaka, Samanga (Lajjalu), Ativisa, Lodhra, Kutaja, Indrayava (Kutaja), Tvaca (Tvak), Jatiphala, Cirabilva, Kanaka bija (Suddhadhattura), Dadimachada (dadima), Samanga (Lajjalu), and Dhataki, Kustha (Rt.),) contains 6 mg of each of theseingredient ingredients and Kesaraja Rasa (bhrngaraja),) andChagidugdha (ajaksira) Q.S. for bhavana [5-11].

Protein is the important part of all cells and tissues. The total protein test measures the total amount of two classes of proteins found in the fluid portion of blood: albumin and globulin. Albumin helps to prevent fluid leakage from blood vessels and globulins are an important part of immune system [39]. Drugs such as estrogens, oral contraceptives, and any drug toxic to the liver, can cause a reduction of the total blood protein levels. Thehighly significant decrease of total protein in the PJB-treated experimental population can be due to liver diseases, andKidney kidney problems.Conditions such as hyperthyroidism and thiamine deficiency may also cause low protein levels in the body[40,41].

A serum albumin test measures the amount of protein in the clear liquid portion of the blood. This test can help determine if a patient personhas liver disease or kidney disease, or if thea person's body is not absorbing enough protein [42].The highly significant increase of

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albumin in the PJB-treated experimental population can also be due to dehydration, but the test is rarely used to diagnose dehydration as the other symptoms are clearer and more obvious. Drugs that increase albumin levels are insulin, growth hormones,osmotic diuretics,mannitol, and anabolic steroids [4443-4645].

Globulins are the key building block of antibodies. Globulins include gamma globulins (antibodies), beta globulins, alpha-2 globulins, and alpha-1 globulins and a variety of enzymes and carrier or transport proteins. Since the gamma fraction usually makes up the largest portion of the globulins, antibody deficiency should always come to mind when the globulin level is low [4746,4847].There is a very highly significant decrease of globulin in the PJB-treated experimental population.Nephrosis, Emphysemaemphysema, Acute acute hemolytic anemia, Liver liver dysfunction, andHypogammaglobulinemiahypogammaglobulinemia lead to low serum globulins level[4443-4645]. Considering the decrease in globulin content along with the noticeable lowering of total protein content in PJB-treated male rats, liver and kidney dysfunction might be a noteworthy point for further study.The liver can function adequately on 20% of liver tissue, thus early diagnosis by lablaboratory methods is difficult. A reversed A/G Ratio ratio may be a helpful indicator[4746,4847]. The normal A/G ratio of albumin to globulin is usually between 1.7-2.2.The significantly high A/G ratio suggests underproduction of immunoglobulins. An A/G ratio higher than 2.2 may indicate decreased thyroid function, low globulin, or an excess of glucocorticoids[4443-4645]. This can also prove to be an illuminating point for further scope of study.

Creatinine, an important part of muscle, is a breakdown product of creatine.The Alaboratory test is performed to measure the amount of creatinine in the blood to evaluate kidney function. In case of abnormal kidney function, creatinine levels will increase in the blood [4948-5554].Theincrease in the creatinine level in the serum of the male ratcould be due to renal insufficiency, decreased renal perfusion or reduced blood flow to the kidneys due to shock, dehydration, congestive heart failure, atherosclerosis, Skeletal skeletal muscle trauma, Ketonemiaor ketonemiaorcomplications of diabetes, infection or autoimmune diseases, prostate disease, kidney stone, orurinary tract obstruction, pyelonephritis, death of cells in the kidneys' small tubes caused by drugs or toxins, or medications (Inhibit inhibit tubular secretion of Creatininecreatinine).Increased creatinine level in the blood suggests that kidney is having a compromised functional state[5655-6160].PJB should be used with caution in those individuals who are carrying any of the risk factors mentioned above.

Blood urea nitrogen (BUN) test is often carried out to check kidney function.BUN Increases increases by 10-20 mg/dl/day, if renal function is hindered, serum creatininelevel is a better measure offor renal function and BUN is reabsorbed at renal tubules [3433].Drugs like such asdiuretics, aminoglycoside antibiotic, ganglionic blocker, angiotensin-converting enzyme inhibitor, cephalosporins, and hypervitaminosis D increaseBUN level in the serum and decrease the amount of urea excreted by the kidneys due tobecause of acute or chronic kidney dysfunction or failure,that which in turnincreases the serum urea level[4443-4645]. So,PJB should be used with caution in those individuals with compromised kidney function as this causes the elevation in serum urea level.

Uric acid is a chemical created when the body breaks down substances called purines, which are nitrogen-containing compounds found in the body in substances such as DNA. Most uric acid is removed from the body by the kidneys and is excreted in the urine; the remainder is eliminated in the stool.If too much uric acid is produced or not enough is excreted, it can accumulate in the body and cause increased levels in the blood (hyperuricemia) [4746,4847].There are Ddrugs that can increase the level of uric acid in the body,like for example,alcohol, ascorbic acid, aspirin, caffeine, cisplatin, diazoxide, diuretics, epinephrine, ethambutol, levodopa, methyldopa, nicotinic acid, phenothiazines, and theophylline[4443-4645].).Thesignificant increase in the uric acid level in the serum of the PJB-treated population may be due tohypoparathyroidism, nephrolithiasis, polycythemia vera,and/or renal failure.

<H1>**CONCLUSION**

From the above data obtained it can be concluded that PJB should not be administered chronically at a higher dose as it may cause kidney disease. Further studies should be done by reducing the dose administered dose.

<H1>**ACKNOWLEDGEMENT**

The authors are thankful to Focused Research on , Department of Pharmacy, and all faculty members and the technical staffs of the Department of Pharmacy, for their kind co-operation. We wouldThe authors express our theirspecial thanks to Mr. for ensuring a constant supply of animals andfollowed byalso for the proper maintenance and care of these animals during all throughout the experimental period.

<TBL_CAP>**Table 1:** Name of the ingredients/herbs used in the preparation of PijusaballiRasa (PJB).

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<T_HEAD>Name of ingredients	Scientific/Common common names	Parts used	Amount used
Sutaka (suddhaparada)	-Mercury(purified)	-	6 g.
Gandhaka (suddha)	-Sulfur(purified)	-	6 g.
Abhra (abhrakabhasma)	-Calcinedpurified mica ash	-	6 g.
Tara (rajatabhasma)	-Silver ash(calcined silver)	-	6 g.
Lauha (bhasma)	-Iron, Cinnabarcinnabar	-	6 g.
Tangana (suddhatankana)	-Borax	-	6 g.
Rasanjana (daruharidra) (Ext.)	*Berberisaristata*	Extract	6 g.
Maksika (bhasma)	Chalcopyrite	-	6 g.
Lavanga (Fl.)	*Syzygiumaromaticum*	Flower	6 g.
Candana (svetacandana) (Ht. Wd.)	*Santalum album*	Wood	6 g.
Musta (musta) (Rz.)	*Cyperusrotundus*	Rhizomes	6 g.
Patha (Rt.)	*Cissampelospareira*	Root	6 g.
Jiraka (Svetajiraka) (Fr.)	*Cuminumcyminum*	Flower	6 g.
Dhanyaka (Fr.)	*Coriandrumsativum*	Flower	6 g.
Samanga (Lajjalu) (Pl.)	*Mimosa Pudica pudica*	Plant	6 g.
Ativisa (Rt.)	*Aconitum heterophyllum*	Root	6 g.
Lodhra (St. Bk.)	*Symplocosracemosa*	Stem Barkbark	6 g.
Kutaja (St. Bk.)	*Holarrhenaantidysenterica*	Stem Barkbark	6 g.
Indrayava (Kutaja) (Sd.)	*Holorrhenaantidysenterica*	Seed	6 g.
Tvaca (Tvak) (St. Bk.)	*Cinnamimumzeylanicum*	Stem Barkbark	6 g.
Jatiphala (Sd.)	*Myristicafragrans*	Seed	6 g.
Cirabilva (Fr. P.)	*Holopteleaintegrifolia*	Fr Patel	6 g.
Kanaka bija (Suddhadhattura) (Sd.)	*Daturastramonium*	Seed	6 g.
Dadimachada (dadima) (Fr. P.)	*Punicagranatum*	Fr Patel	6 g.
Samanga (Lajjalu) (Pl.)	*Mimosa Pudica*	Plant	6 g.
Dhataki (Fl.)	*Woodfordiafruticosa*	Flower	6 g.
Kustha (Rt.)	*Saussurealappa*	Root	6 g.
Kesaraja Rasa (bhrngaraja) (Pl.)	*Eclipta alba*	Plant	Q.S. for bhavana
Chagidugdha (ajaksira)	-Goat's milk		Q.S. for bhavana

<TBL_CAP>**Table 2:**Effect of PijusaballiRasa (PJB) on Total total Serum serum Proteinprotein, Albuminalbumin, Globulin globulin content, and albumin/globulin (A/G) ratio in Male male Ratsrats.

<T_HEAD>Parameters	Control	PJB	p values	% Change
Total Protein protein(TP)	54.2500 ± 1.01330	49.1250 ± 1.00778	0.003	↓9.45%
Albumin	27.8750 ± 0.78916	34.7500 ± 1.98881	0.010	↑24.66%
Globulin	26.3750 ± 1.76208	14.3750 ± 2.33710	0.001	↓45.50%
A/G ratio	1.1054 ± 0.10556	3.0419 ± 0.60785	0.015	↑175.19%

<T_FOOT>↑: increase, ↓: decrease; *p* ≤ 0.05, **p** ≤ 0.01, ***p*** ≤ 0.001

<TBL_CAP>**Table 3:**Effect of PijusaballiRasa (PJB) on Creatininecreatinine, blood urea nitrogen (BUN), BUN/Creatinine creatinine ratio, and Uric uric Acid acid level in male rats.

<T_HEAD>Parameters	Control	PJB	P pvalues	% Change
Creatinine	0.8250 ± 0.03660	0.8875±.02950	0.205	↑7.58%
Blood Urea Nitrogen (BUN)	11.0806 ± 0.53553	12.3248 ± 0.75419	0.200	↑11.23%
BUN/Creatininecreatinine	13.5228 ± 0.66075	13.9944 ± 1.01103	0.702	↑3.49%
Uric Acidacid	1.9875 ± 0.08332	2.4875 ± 0.15861	0.014	↑25.16%

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