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EVALUATION OF NEPHROPROTECTIVE ACTIVITY OF KATAKABEEJA YOGA AGAINST ASPIRIN-INDUCED NEPHROTOXICITY IN WISTAR RATS

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ABSTRACT

Drug-induced toxicity is the major concern in the present Era, particularly with Hepato and Nephrotoxicity. Drug-induced renal failure (RF) accounted for 20% in India. As there is an increasing number of potent therapeutics drugs like – NSAID's (Aspirin), Antibiotics, chemotherapy agents etc. *Katakabeeja Yoga* is mainly indicated in *Prameha Chikitsa* according to Yogaratnakar. *Kataka* (*Strychnos potatorum*. Linn) is *Vishaghna, Ashmari, Prameha, Visha* etc. *Kataka* - Independently have potent Antioxidant, Osmotic diuretic activity. Hence the present study was aimed to evaluate the Nephroprotective activity of *Katakabeeja Yoga* against Aspirin-induced Nephrotoxicity in Wistar rats. *Katakabeeja Yoga* was prepared after authenticating procured raw drugs and analyzed for preliminary physicochemical, organic and inorganic tests. Either sex Wistar rats weighing 150 – 200 g were selected and randomized into three groups (each group 6 no.) like Normal, Aspirin-induced, or *Katakabeeja Yoga*

treated. Toxicity with Aspirin 100mg/kg orally for 15 days. In the treated group *Katakabeeja yoga* 0.216g (216mg) was received after administration of Aspirin for 15 days and sacrificed on the 16th day. Before and end of the study, the blood sample was collected for estimation of biomarkers like Serum Creatinine, urea and electrolytes. The kidney was kept in a 10% formalin solution and sent for histopathology studies. Data were analyzed by one way ANOVA and Tukey's multiple post hoc procedures. The Aspirin group showed a significant rise in serum Creatinine, and urea followed by a decrease the urine output. *Katakabeeja Yoga* significantly reduced the serum Creatinine and urea followed by an increase in the urine output may have *Katakabeeja* potent antioxidant, osmotic diuretic activity. The study established that *Katakabeeja Yoga* possesses a durable Nephroprotective effect against Aspirin-induced Nephrotoxicity.

Keywords: Nephroprotective, *Kataka*, Nephrotoxicity

INTRODUCTION

Drug-induced toxicity is the major concern in the present Era, particularly with Hepato and Nephrotoxicity. There is an increasing number of potent therapeutic drugs like Aminoglycosides, Antibiotics, NSAID's (Ibuprofen, Indomethacin, Aspirinetc.).[1]

Oxidative damage is possibly an important mechanism in the pathogenesis of Aspirin nephrotoxicity. It was reported that Aspirin exerts nephrotoxicity through a reduction in the production of antioxidants [2].

Inhibition of the synthesis of renal prostaglandins by NSAIDs (Aspirin) may affect renal function. The mechanism involves inhibition of vasodilator prostaglandin synthesis from arachidonic acid which leads to vasoconstriction and a decrease in glomerular capillary pressure, resulting in a prompt decline in glomerular filtration rate. This form of renal failure, which is characterized by increased serum levels of Creatinine, urea and potassium, is often sudden and is completely reversible with prompt discontinuation of NSAID. When unopposed, this may lead to acute tubular necrosis (ATN), which can also result in ARF [3].

In our classics explained *Garavisha* is intentionally in the olden days then unintentionally now. It is a condition explained by Acharaya which arises due to the entry of *visa* which has been fabricated due to a mixture of non-poisons or poisonous substances or medicines like *bhasma's.* When a person is exposed to these kinds of poisons, maybe for one time or longer duration, depending on the potency and nature of the poison exposed or after a long interval suffer from several disorders as per the affinity of poisons exposed [4].

The formulation *Katakabeeja Yoga* is explained in the context of *Prameha* [5]. The chief component of this formulation is *Kataka*.

Kataka (Strychnos Potatorum. Linn*)* is explained under ***Vishaghna Dashamani's*** [6] and used in ***Ashmari*** [7], ***Visha***, and ***Prameha*** [5] etc. *Kataka* has reported potent antioxidant, Osmotic diuretic activity etc.

Aims and Objectives – To evaluate the Nephroprotective activity of *Katakabeeja Yoga* against Aspirin-induced Nephrotoxicity in Wistar rats.

Material and Methods:

The study was conducted after obtaining the approval of the Institutional Animal Ethics Committee (BMK/IAEC/Res-02/2014).

Animals:

18 Healthy sex Wistar rats weighing between 150-200 g were used in the study. They were housed individually, and they were provided with standard feeds and water *ad libitum* during the experimental study (CPCSEA Guidelines). All Experimental rats were kept at an ambient temperature of 25°C ± 5°C and 45-55% relative humidity with 12 hr natural light and dark cycle.

Study Design:

The animals were randomly allocated into three groups of six animals each. Group-I control (Distilled water), Group-II Aspirin 100mg/kg/orally daily [3] and Group-III *Katakabeeja Yoga*.

Groups	No. of Animals in groups	Dose	Duration
Group A	n = 6	Control group	15 days
Group B	n = 6	Aspirin 100mg/kg/orally	15 days
Group C	n = 6	*Katakabeeja yoga*(216mg/200g) + Aspirin 100mg/kg/orally	15 days

PARAMETERS OF EXPERIMENTAL STUDY:

Effect of *Katakabeeja Yoga* in Aspirin-induced nephrotoxicity in Wistar Rats

i. **General observation**- Animals of all groups were observed for their food intake and water intake, general activity, body weight, urine output throughout the experimental study.

ii. **Blood investigation**-1st, 8th and 15th day all animals were kept under observation for 24 hours. On 16th the day animals were anaesthetized by Diethyl Ether and blood was drawn through the retro-orbital region by pricking microcapillary tube number 100 mm (Borosilicate glass with both ends open) and collected in labelled vials. Blood was sent to Jeevan Diagnostic Center, Belgavi for biochemical investigations.

Biochemical investigations: Blood was collected in a plain vial and subjected to performing biochemical parameters like Serum Creatinine, Serum urea, and Serum electrolyte.

iii. **Histopathological investigations**- Kidney was collected immediately after sacrificing by anaesthesia with diethyl ether and cleaned of extraneous tissue and transferred to 10% formalin solution in separate labelled containers sent for Jeevan Diagnostic Laboratory, Belgavi for Histopathological study.

STATISTICAL ANALYSIS

All results are expressed as the mean ± SD. One way ANOVA was applied for testing the significant difference between three groups at each time point. Tukeys multiple post hoc procedures were applied to see the significant difference between pairs of two groups.

RESULTS:

Table 1: Statistical interpretation of SERUM CREATININE at the confidence level of 95% ($p<0.05$)

SERUM CREATININE			
	Normal	Aspirin	Aspirin+Katakabeeja Yoga
Mean ± SD	0.9528±0.08970	1.758±0.2157	1.153± 0.1428
Significance	-	-	**
P-VALUE		< 0.0001	
F		82.10	

*Note: *p<0.05*

Pairwise comparisons of three groups by Tukey's HSD

GROUPS	SERUM CREATININE
C vs AKY (P Value)	< 0.0001***
C Vs A (P Value)	0.0150**
AKY Vs A (P Value)	0.0020**

**p<0.05*

Table 2: Statistical interpretation of SERUM CHLORIDE at the confidence level of 95% (p<0.05)

SERUM CHLORIDE			
	Normal	Aspirin	Aspirin+Katakabeeja Yoga
Mean ± SD	105.3 ± 1.748	108.1 ± 2.968	107.9 ± 2.605
Significance	-	-	**
P-VALUE		0.0083	
F		8.720	

*Note: *p<0.05*

Pairwise comparisons of three groups by Tukey's HSD

GROUPS	SERUM CHLORIDE
C vs AKY (P Value)	0.0166**
C Vs A (P Value)	0.0407**
AKY Vs A (P Value)	0.9899 (NS)

**p<0.05*

Table 3: Statistical interpretation of SERUM POTASSIUM at the confidence level of 95% (p<0.05)

SERUM POTASSIUM			
	Normal	Aspirin	Aspirin+Katakabeeja Yoga
Mean ± SD	5.717 ± 0.2765	7.475 ± 0.4311	6.897 ± 0.2444
Significance	-	-	***
P-VALUE		0.0002	
F		35.68	

*Note: *p<0.05*

Pairwise comparisons of three groups by Tukey's HSD

GROUPS	SERUM POTASSIUM
C vs AKY (P Value)	0.0026**
C vs A (P Value)	0.0031**
AKY vs A (P Value)	0.0538(NS)

**p<0.05*

Table 4: Statistical interpretation of SERUM UREA at the confidence level of 95% (p<0.05)

SERUM UREA			
	Normal	Aspirin	Aspirin+Katakabeeja Yoga
Mean ± SD	37.44 ± 2.834	49.47 ± 4.024	43.28 ± 3.862
Significance	-	-	**
P-VALUE		0.0019	
F		17.22	

*Note: *p<0.05*

Pairwise comparisons of three groups by Tukey's HSD

GROUPS	SERUM UREA
C vs AKY (P Value)	0.0117*
C vs A (P Value)	0.0383*
AKY vs A (P Value)	0.0456*

**p<0.05*

Table 5: Statistical interpretation of SERUM SODIUM at the confidence level of 95% (p<0.05)

SERUM SODIUM			
	Normal	Aspirin	Aspirin+Katakabeeja Yoga
Mean ± SD	141.4 ± 2.172	148.5 ± 1.792	149.1 ± 2.417
Significance	-	-	***
P value	0.0007		
F	22.30		

*Note: *p<0.05*

Pairwise comparisons of three groups by Tukey's HSD

GROUPS	SERUM SODIUM
C vs AKY (P Value)	0.0115*
C vs A (P Value)	0.0011**
AKY vs A (P Value)	0.8970(NS)

**p<0.05*

Table 6: Statistical interpretation of URINE OUTPUT 1ST DAY at the confidence level of 95% (p<0.05)

URINE OUTPUT 1ST DAY			
	Normal	Aspirin	Aspirin+Katakabeeja Yoga
Mean ± SD	4.467 ± 1.638	3.400 ± .09716	4.833 ± 1.169
Significance			
P value	0.1136		
F	3.107		

*Note: *p<0.05*

Pairwise comparisons of three groups by Tukey's HSD

GROUPS	URINE OUTPUT 1ST DAY
C vs AKY (P Value)	0.1819
C Vs A (P Value)	0.8823
AKY Vs A (P Value)	0.0708

**p<0.05*

Table 7: Statistical interpretation of URINE OUTPUT 8TH DAY at the confidence level of 95% (p<0.05)

URINE OUTPUT 8th DAY			
	Normal	Aspirin	Aspirin+Katakabeeja Yoga
Mean ± SD	5.367 ± 1.274	3.383 ± 0.8565	7.733 ± 1.108
Significance			
P value	0.0032		
F	22.90		

*Note: *p<0.05*

Pairwise comparisons of three groups by Tukey's HSD

GROUPS	URINE OUTPUT 8TH DAY
C vs AKY (P Value)	0.1274(ns)
C Vs A (P Value)	0.0006***
AKY Vs A (P Value)	0.0039**

**p<0.05*

Table 8: Statistical interpretation of URINE OUTPUT 15th DAY at the confidence level of 95% (p<0.05)

URINE OUTPUT 15th DAY			
	Normal	Aspirin	Aspirin+Katakabeeja Yoga
Mean ± SD	6.783 ± 0.8998	2.100 ± 1.661	6.950 ± 3.505
Significance			
P value		0.0081	
F		10.23	

*Note: *p<0.05*

Pairwise comparisons of three groups by Tukey's HSD

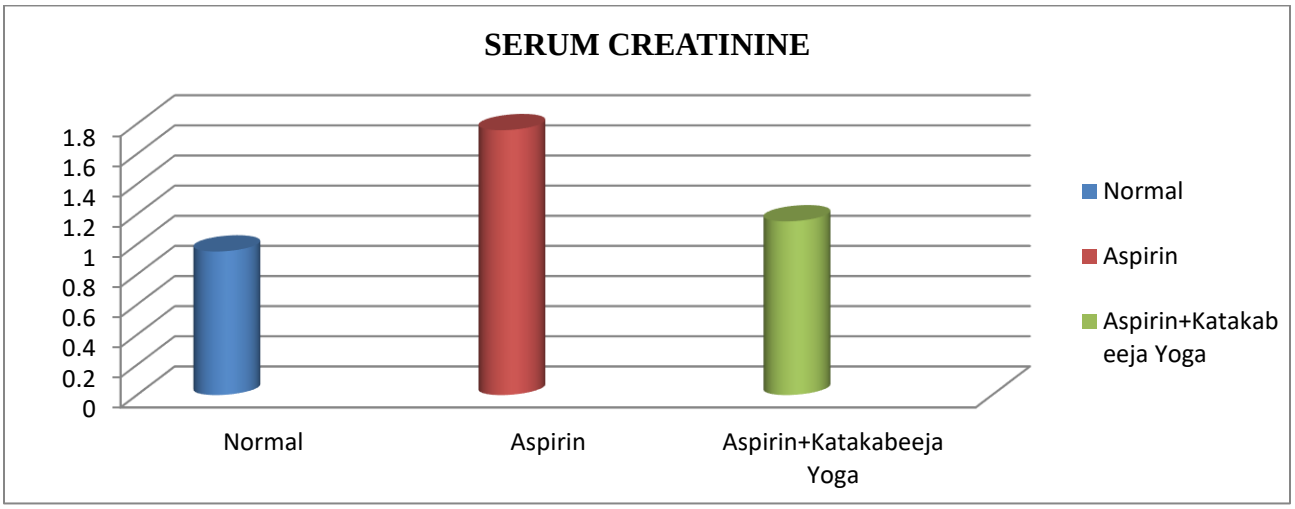
GROUPS	URINE OUTPUT 15TH DAY
C vs AKY (P Value)	0.0087
C Vs A (P Value)	0.9929
AKY Vs A (P Value)	0.0227

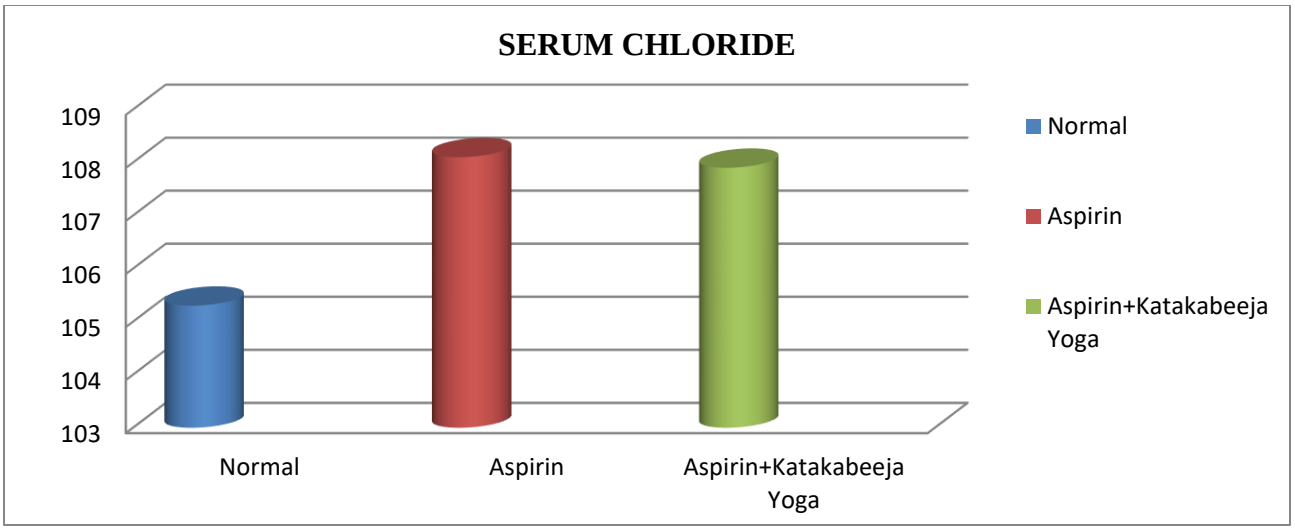
**p<0.05*

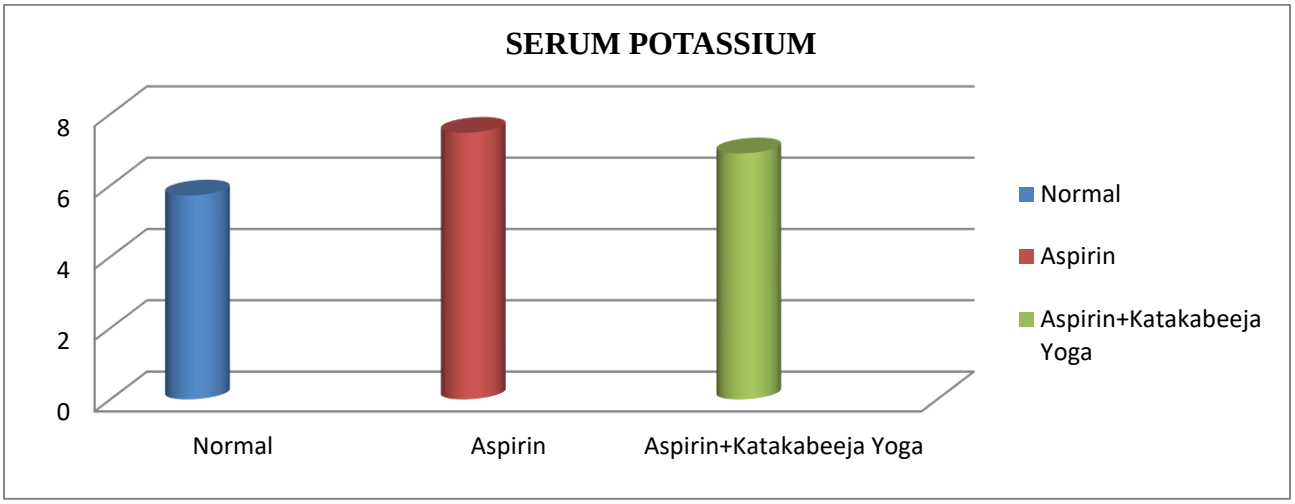
HISTO – PATHOLOGY OF KIDNEY:

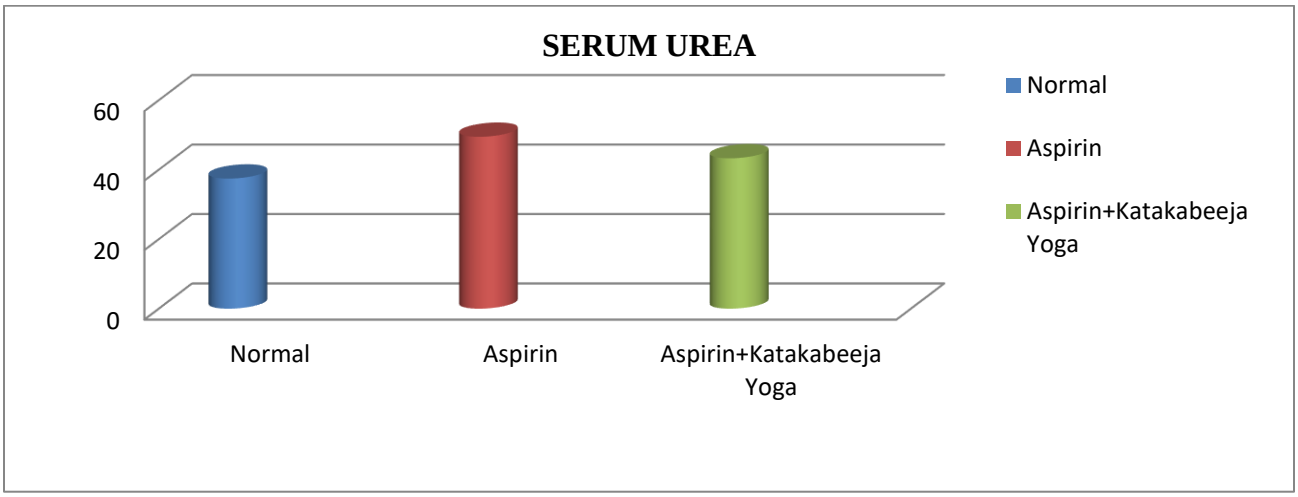
Sl.No.	Microscopy	Normal	Aspirin	Katakabeeja yoga + Aspirin
1	Tubular congestion	++	+++	++
2	Loss of Brush Border	-	+	+
3	Cytoplasmic Vacuoles	-	+	-
4	Tubular Necrosis	-	+	+
5	Glomerular congestion	++	++	++
6	Interstitial oedema	-	+	-
7	Interstitial Haemorrhage	-	++	+
8	Peritubular inflammation	-	+++	+

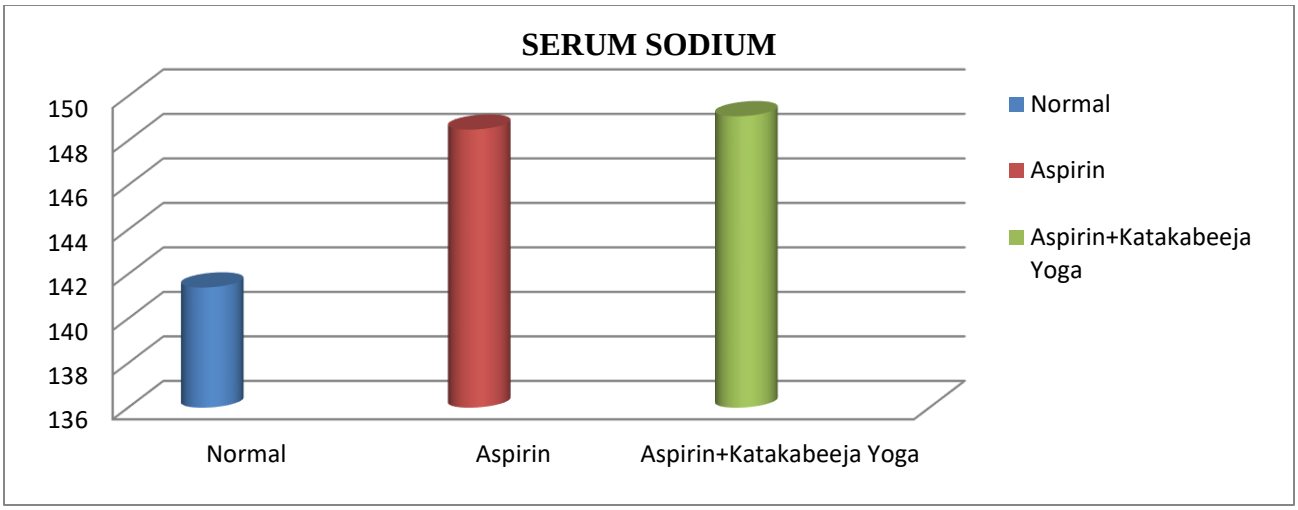
(Note: + - Mild, ++ - Moderate, +++ - Severe)

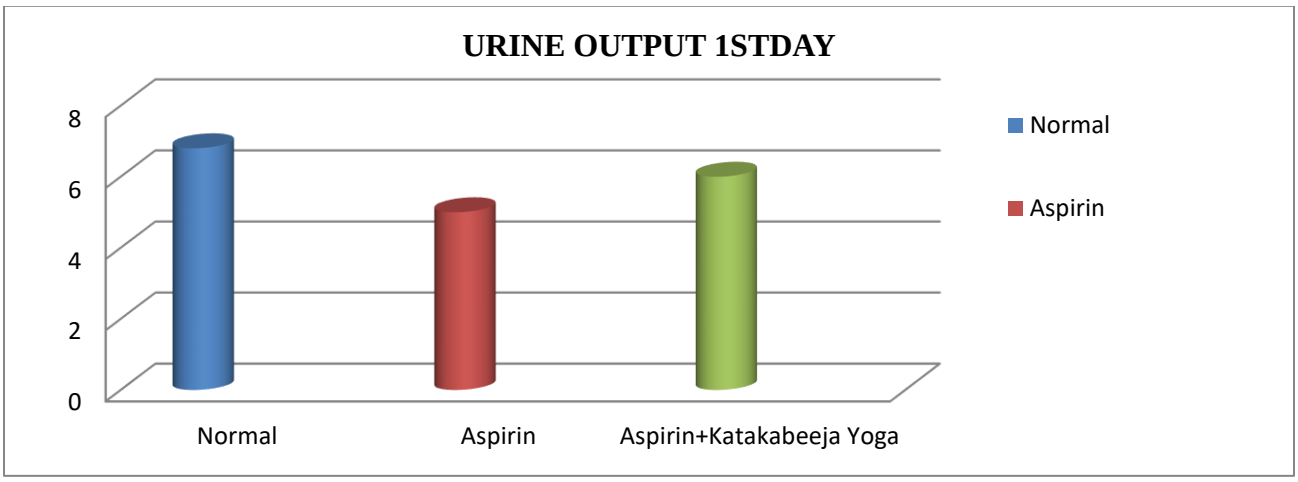


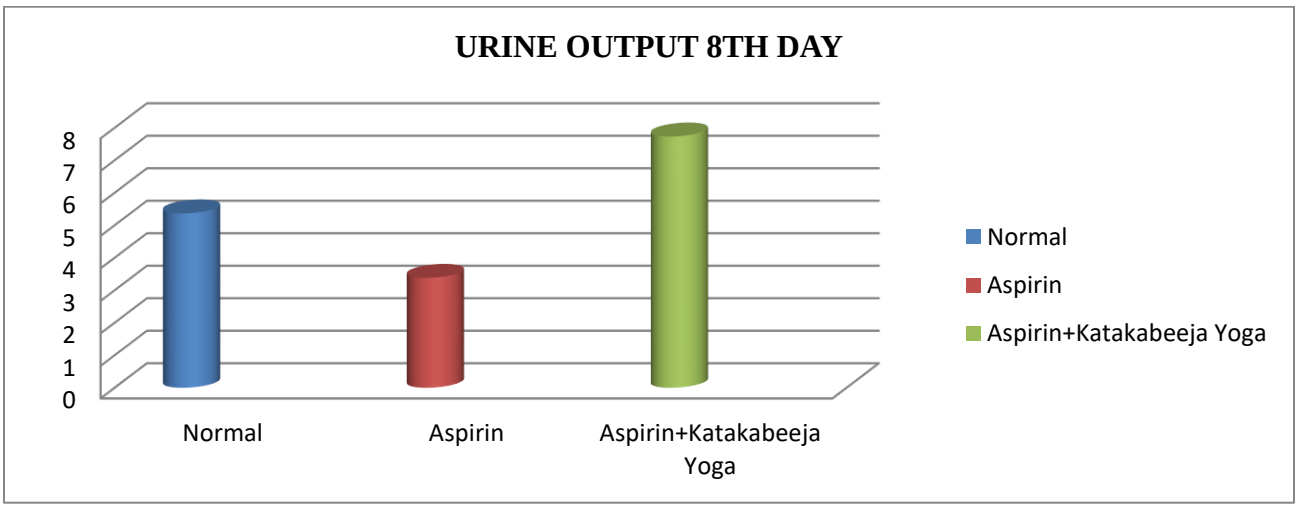

SERUM CHLORIDE
109
108
107
106
105
104
103
Normal
Aspirin
Aspirin+Katakabeeja Yoga
Normal
Aspirin
Aspirin+Katakabeeja Yoga

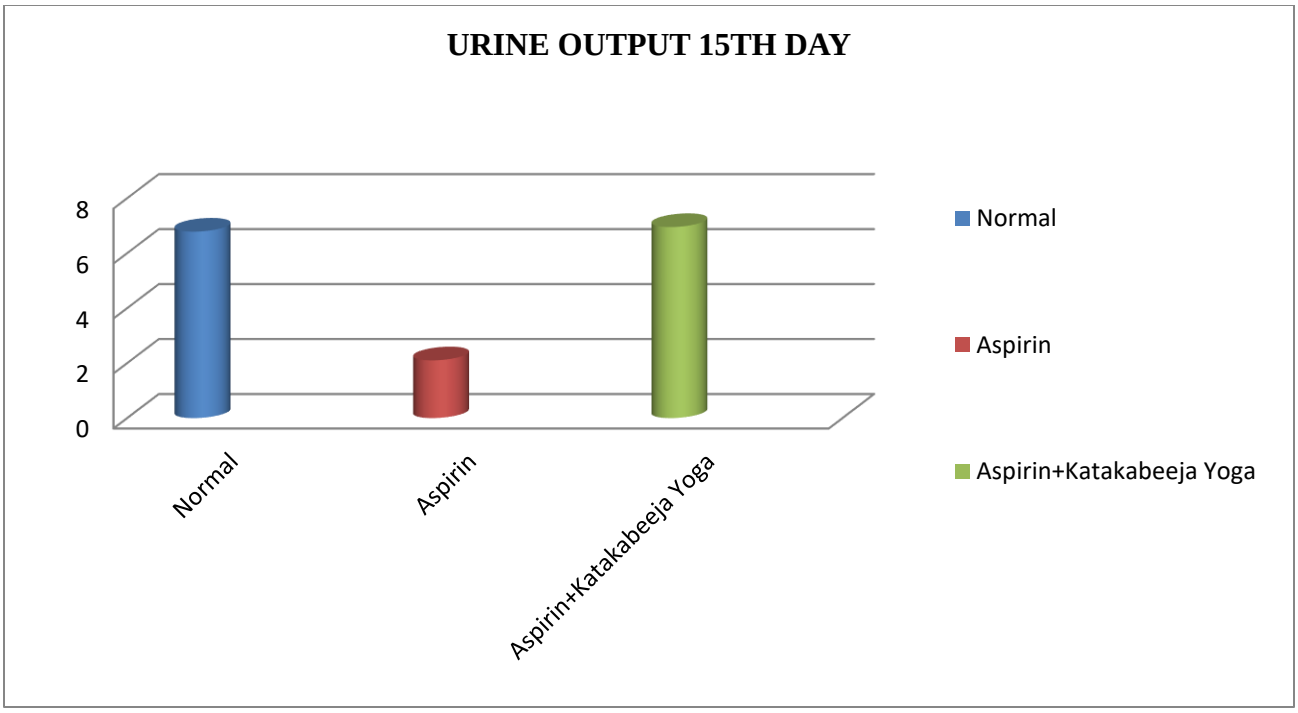

SERUM POTASSIUM
8
6
4
2
0
Normal
Aspirin
Aspirin+Katakabeeja Yoga
Normal
Aspirin
Aspirin+Katakabeeja Yoga


SERUM UREA
60
40
20
0
Normal
Aspirin
Aspirin+Katakabeeja Yoga
Normal
Aspirin
Aspirin+Katakabeeja Yoga

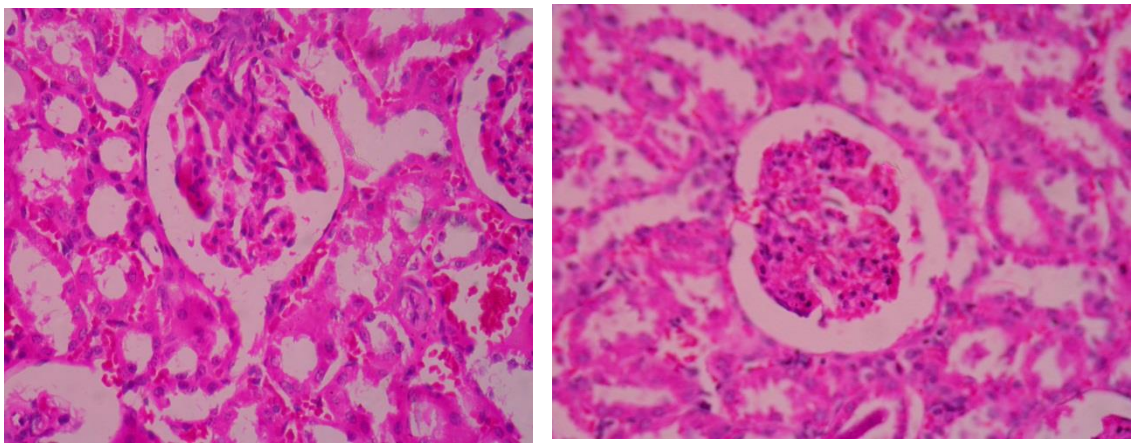

SERUM SODIUM
150
148
146
144
142
140
138
136
Normal
Aspirin
Aspirin+Katakabeeja Yoga
Normal
Aspirin
Aspirin+Katakabeeja Yoga


URINE OUTPUT 1STDAY
8
6
4
2
0
Normal
Aspirin
Aspirin+Katakabeeja Yoga
Normal
Aspirin

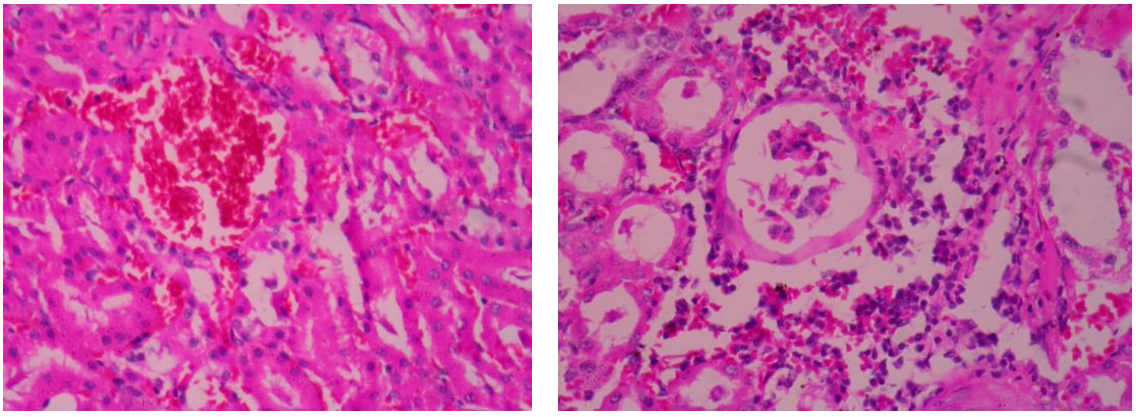

URINE OUTPUT 8TH DAY
8
7
6
5
4
3
2
1
0
Normal
Aspirin
Aspirin+Katakabeeja Yoga
Normal
Aspirin
Aspirin+Katakabeeja Yoga



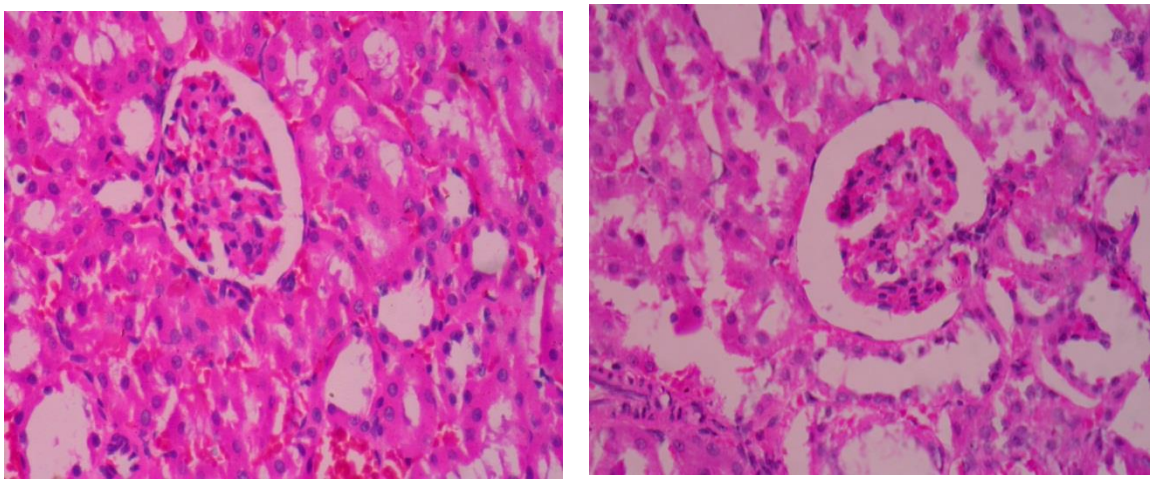
Group A – Control (40 X)



Group B – Aspirin (40 X)



Group C – Katakabeeja Yoga (40 X)



DISCUSSION

Katakabeeja yoga is a compound preparation that is mentioned in the context of *PramehaChikitsa* [5]. This preparation mainly contains *Katakabeeja, Takra* and *Madhu.*

Katakabeeja has been in detail researched in relevance to Antidiabetic activity [8], Antioxidant [9], Anti-inflammatory activity [10], Analgesic activity [11], Antinociceptive and antipyretic effect of seeds [12], Hepatoprotective and antioxidant actions [13], and Diuretic activity of seeds [14].

Aqueous and Alcoholic extract of *Katakabeeja* contains Reducing sugars, Steroids, Cardiac and Saponin glycosides, Alkaloids, Tannins, Calcium, Sodium, Iron, and Nitrates. Among these Saponin might have reduced the inflammation due to Anti-inflammatory activity **[15],** Tannins have haemostatic properties, anti-inflammatory activity (C. Hartisch et al), Calcium – Helps for clotting mechanism and stability of the cell membrane **[16]**. Nitrates – The most prominent action is relaxing vascular smooth muscles and redistribution of blood flow to an ischemic area **[17]**.

URINE OUTPUT:

A significant difference ($p < 0.005$) was evidenced in Urine Output between the groups from 1st day, 8th day till day 15th respectively between the Normal group **(4.467 ± 1.638, 5.367 ± 1.274, and 6.783 ± 0.8998)** and Aspirin group **(3.400 ± 0.9716, 3.383 ± 0.8565 and 2.100 ± 1.661)** and also between Aspirin group (**3.400 ± 0.9716, 3.383 ± 0.8565 and 2.100 ± 1.661)** and *Katakabeeja Yoga* group **(4.833 ± 1.169, 7.733 ± 1.108 and 6.950 ± 3.505).** When compared between the Normal group **(4.467 ± 1.638, 5.367 ± 1.274, and 6.783 ± 0.8998)** and *Katakabeeja Yoga* group **(4.833 ± 1.169, 7.733 ± 1.108 and 6.950 ± 3.505)** the volume of Urine Output is the same which confirms the diuretic activity of *Katakabeeja*. The increase of cations in the urine on treatment with *Katakabeeja* (Strychnos *Potatorum* Linn). This effect supports the use of the *Katakabeeja* (*Strychnos Potatorum.* Linn*)* as a diuretic in folk remedies **[14]**.

UREA:

The *Katakabeeja Yoga* treated group has decreased in the Urea level compared with Aspirin treated group **(43.28 ± 3.862),** when compared with *the Katakabeeja Yoga* group &Normal group **(49.47 ± 4.024)** it shows significance. The Aspirin group has raised the Urea level compared with the Normal group with **(37.44 ± 2.834).** Because *Katakabeeja* has nitrates [17] and antioxidant [9], anti-inflammatory activity [10].

CREATININE:

The *Katakabeeja Yoga* treated group has decreased in a higher Creatinine level compared with Aspirin treated group **(1.153 ± 0.1428),** when compared with *the Katakabeeja Yoga* group &Normal group **(1.758 ± 0.2157)** it shows significance. The Aspirin group has raised the Creatinine level compared with the Normal group with **(0.9528 ± 0.089).** Because *Katakabeeja* has nitrates [17] and antioxidant [9], anti-inflammatory activity [10].

Histopathological Reports: -

KIDNEY: Tubular congestion, peritubular inflammation, Tubular necrosis in the Kidney showed more damage in the Aspirin group (+++) when compared to the *Katakabeeja Yoga* group (++). Cytoplasmic vacuole, glomerular congestion, interstitial haemorrhage showed mild damage in the Aspirin group (++) when compared to the *Katakabeeja* group (+). Interstitial oedema, widening of Bowmen space (+) but is not present in *Katakabeeja Yoga* group.

CONCLUSION

Katakabeeja Yoga has significantly increased Urine output and reduced Sr. Urea & Sr. Creatinine. The serological and Histopathological changes show that the *Katakabeeja Yoga* has got protective effect against Aspirin-induced nephrotoxicity in Wistar rats. There was no significant change in the levels of Serum Potassium, Sodium, and Chloride.

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