

Effects of Dried *Aloe Vera* Gel and Diclofenac on Sodium and Potassium Homeostasis: An Experimental Study on Hypertensive Rats

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ABSTRACT

Background: Anti-inflammatory role of *Aloe vera* gel is well established. Diclofenac is extensively used for acute and chronic inflammation. The present study was conducted to compare dried *Aloe vera* gel and diclofenac effects on sodium and potassium balance in hypertensive rats.

Material and Methods: This experimental study was conducted at Sargodha Medical College from May to November 2016. Twenty-four healthy male Sprague Dawley rats 7-8 weeks of age were included in study. Any unhealthy-looking rat was excluded from the study. Rats were equally and randomly divided into four groups Normal control (group A), Model control (group B), *Aloe vera* (group C) & Diclofenac (group D). Hypertension was induced by a 20 % sucrose diet in all groups except group A in 8 weeks' time. Group B, C & D received distilled water and *Aloe vera* dried gel 400 mg/kg & diclofenac powder 12 mg/kg body weight respectively orally between 8 to 10 weeks. Serum and urine analysis was performed for hematocrit, sodium, and potassium concentrations at zero, eight and ten weeks. Twenty-four-hour urinary sodium excretion was calculated. Data was analyzed using Graph Pad Prism version 6.

Result: After 2-week administration of *aloe vera* and diclofenac powder, serum potassium significantly decreased in Group C ($p < 0.001$) while increased in Group B and D ($p < 0.001$) as compared to group A. Urinary sodium concentration and excretion increased significantly in Group C ($p < 0.01$) as compared to Group A whereas result of Group D was insignificant. No significant change in serum sodium and hematocrit of any group was observed.

Conclusion: *Aloe vera* causes less sodium retention than diclofenac but decreases serum potassium contrary to the effect of diclofenac in hypertensive rats.

Keywords: *Aloe vera*, Diclofenac, Electrolyte, Hematocrit, Hypertension

Authors' Contribution:

⁴Conception; Literature research; manuscript design and drafting; ^{1,2}Critical analysis and manuscript review; ³Data analysis; Manuscript Editing.

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Introduction

NSAIDs are the most prescribed agents in Pakistan for controlling inflammation, pain and fever. The main action of these agents is to suppress prostaglandin (PG) synthesis; by inhibiting the

enzyme cyclooxygenase (COX-I&II). COX-I enzyme of kidneys plays a physiological role and controls hemodynamic and glomerular filtration rate (GFR), while COX-II is an inducible enzyme responsible for

cell injury or inflammation. This enzyme is also present in kidneys and affects electrolytes and water excretion hence regulates intravascular volume. Decreased activity of cyclooxygenase enzymes by NSAIDs causes hyperkalemia and sodium and water retention that causes edema hypertension, and kidney damage.^{1,2}

NSAIDs other than affecting the kidneys also cause gastric and duodenal ulceration, exacerbate asthma symptoms, and increase bleeding tendency. NSAIDs like diclofenac have more potential to harm older people due to renal and cardiovascular risk. They carry a threat of chronic decrease of GFR as well as acute kidney damage.³ According to Liew.*et al.*, continuous use of NSAIDs is associated with the risk of hypertension in 12 percent of individuals as compared to non-use or limited use of NSAIDs.⁴

Aloe vera, a water-storing and drought-tolerant plant has many therapeutic effects including anti-inflammatory, immunomodulatory, hypoglycemic, anticancer, gastro-protective and antimicrobial properties. Due to these vast pharmacological effects; *Aloe vera* has been employed for several commercial applications.⁵ It can be separated into two basic products; latex, a bitter yellow exudate derived from the outer skin of the leaves which occupy approximately 20–30% of the weight of the whole leaf, and gel, which is a transparent mucilage material derived from the pulp of the leaves.⁶ This mucilaginous part of *Aloe vera* is traditionally used in different inflammatory disorders.⁷

The anti-inflammatory activity of this medicinal plant justifies its use in dermal inflammatory disorders and joint diseases, particularly in elderly patients. In this age group, the use of NSAIDs is limited because of their documented adverse effect on sodium & water retention and electrolyte imbalance. There is insufficient data on safety of *Aloe vera* regarding sodium and potassium homeostasis especially in hypertensive subjects.

The purpose of this study is to evaluate the use of *Aloe vera* and its comparison with diclofenac on the hematocrit and electrolyte (sodium and potassium)

balance of hypertensive rats. This research can provide data on safety profile of *Aloe vera* to be used for future human studies on hypertensive patients.

Material and Methods

After approval from the ethical committee, this animal experimental study was conducted at Sargodha Medical College between May and November 2016. Twenty-four *Sprague Dawley* rats weighing between 235–380 g, according to inclusion criteria of 7-8 weeks age and male gender were obtained from the University of Agriculture Faisalabad. Unhealthy-looking rats were excluded. Rats were randomly divided by lottery method into four equal groups: Normal control (Group A), Model Control (Group B), *Aloe vera* group (Group C) and Diclofenac group (Group D). They were kept in the college animal facility in iron cages for two weeks for acclimatization. Room temperature was maintained at 25±5°C. A light and dark cycle of 12 hours was followed, and animals were given free access to food and water. Rats in Group A were given normal rat chow throughout the study period, whereas all the other groups were given normal rat chow containing sucrose (20% w/w) to induce hypertension,⁸ which was induced in all three groups in eight weeks. Systolic blood pressure ≥ 140 mm Hg was considered hypertension⁹. After induction of hypertension at 8th week, Group B was given distilled water 0.5ml, and Group C was given *Aloe vera* gel powder 400 mg/kg body weight,¹⁰ and Group D was given diclofenac powder 12 mg/kg body weight by the oral route as a single morning dose for two weeks.¹¹

Plants were purchased from a local nursery and identified by the Botany Department of Sargodha University. After washing the *Aloe vera* leaves and draining the yellow juice, the pulp was removed, mixed in a blender, filtered, air-dried and the resultant dried gel was stored at 4°C.¹⁰ Yield with reference to the whole leaf was 0.14%. The fresh

solution was prepared daily by dissolving 400 mg in 5 ml distilled water.

The body weight and blood pressure of animals were recorded at baseline and then weekly throughout the study. Systolic blood pressure was measured by tail-cuff,⁸ using a non-invasive blood pressure controller (ML125R) attached to the computer-based data recording system (Power lab).

Twenty-four-hour urine was collected in a glass container by keeping each animal in a separate cage at 0, 8, and 10 weeks. Urine sodium concentration and volume were measured and 24-hour urinary excretion was calculated. After urine collection, two ml of blood was drawn through cardiac puncture; one ml blood was put in EDTA for determination of hematocrit and one ml in gel & clot activator vacutainer. To separate serum, blood was centrifuged at 5000 rpm for three minutes. Serum sodium and potassium levels were estimated by a flame photometer (SEAC P-10) and hematocrit by a hematology analyzer (Sysmex KX-21).

Data was analyzed using Graph Pad Prism version 6. Normality was tested by the Shapiro-Wilk normality test and data was presented as mean ± SD. Normally distributed data was compared using ANOVA. Changes in parameters at different times in each group were compared by t-test. Post hoc Tukey's test was applied for comparison among groups. A p-value of ≤0.05 was considered significant.

Results

During the first 8 weeks, body weight, as well as systolic blood pressure, increased significantly (p value < 0.001) in groups receiving sucrose diet (B, C & D) as compared to Group A while after two weeks, blood pressure increased by 2, 4, 3 and 17 mm Hg in groups A, B, C and D respectively. However, no significant change was seen in hematocrit of any group during the study period (Table 1). Serum sodium concentration remained within the normal range with non-significant differences in readings throughout the study

Table I: Effect of Aloe vera gel and diclofenac on hematocrit, serum sodium and urine volume of hypertensive rats (n=6)

Groups	Hematocrit (%)			Serum Na (mEq/L)			Urine Vol. (ml)		
	0 Week	8 Weeks	10 Weeks	0 Week	8 Weeks	10 Weeks	0 Week	8 Weeks	10 Weeks
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
Normal Control(A)	37.83±3.06	38±3.9	38.5±3.73	120.83±14.2	118.17±8.38	123±12.17	5.77±1.05	5.83±0.41	5.87±0.60
Model Control(B)	37.67±2.8	39±3.29	38.5±2.43	117.83±3.37	116.67±16.94	117.67±6.62	5.72±1.80	5.70±0.28	5.77±0.23
Aloe vera (C)	36.67±3.39	39.33±6.22	38.67±4.27	119.33±7.31	107.33±30.16	124.33±38.73	5.40±2.69	5.50±0.35	5.40±0.94
Diclofenac (D)	37.17±2.93	39.5±3.45	37.17±2.48	125.17±11.07	118±4.24	115.83±13.14	5.63±2.37	5.60±0.51	5.17±0.59
ANOVA	0.909	0.934	0.850	0.612	0.685	0.884	0.990	0.518	0.234

Serum Potassium Concentration: Analysis by t-test within each group between 8 to 10 weeks revealed that serum potassium significantly decreased in *Aloe vera* group (Group C) and increased in diclofenac (Group D) and model control (Group B) groups with p-values < 0.001, < 0.001 and 0.008

respectively. At the end of study, serum potassium was significantly higher in model control and diclofenac groups as compared to normal control, while that of *Aloe vera* group was significantly lower versus all other groups as calculated by Tukey's test (Figure 1).

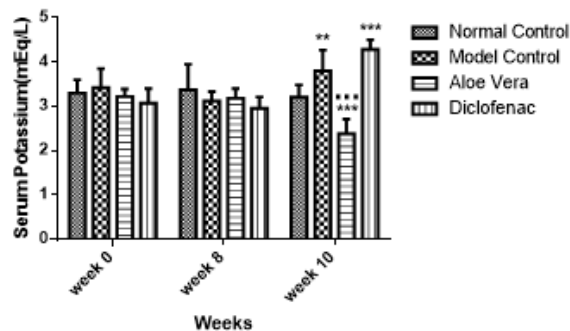


Figure 1: Effect of Aloe vera gel and diclofenac on serum potassium concentration (Mean±SD) of hypertensive rats (n=6). Significance between groups calculated by Tukey's test.

*** p value <0.001 Versus Normal Control Group (A)

** p value <0.01 Versus Normal Control Group (A)

••• p value <0.001 Versus Model Control (B) & Diclofenac Group (D)

Urinary Sodium Concentration: Analysis by t-test within each group between 8 to 10 weeks revealed that urinary sodium concentration increased significantly in model group only (p-value 0.038). At the end of study, urinary sodium concentration was highest in model group, followed by *Aloe vera*, diclofenac and normal group (Figure2).

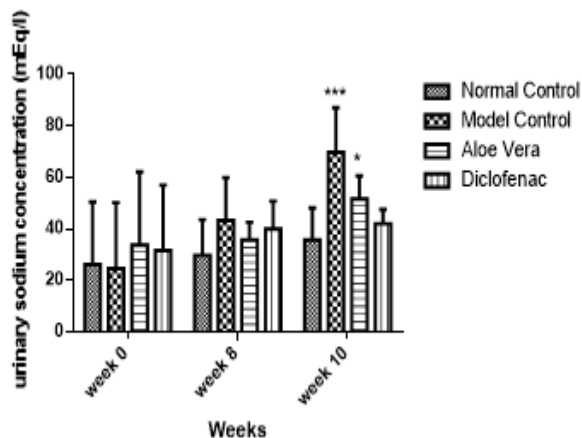


Figure 2: Effect of Aloe vera gel and diclofenac on urinary sodium concentration (Mean±SD) of hypertensive rats (n=6) Significance between groups calculated by Tukey's test.

*** p value <0.001 Versus Normal Control (A) & Diclofenac Group (D)

* p value <0.01 Versus Normal Control (A) & Model control Group (B)

Urinary volume was statically similar in all groups at all reading times (Table 1)

Twenty-four Hour Urinary Sodium Excretion: Results were parallel to urinary sodium concentration, i.e., a significant increase from 8-10 weeks period in model group with p-value 0.016(t-test). At end of 10th week, it was highest in model group followed by *Aloe vera*, diclofenac and normal group (Figure 3).

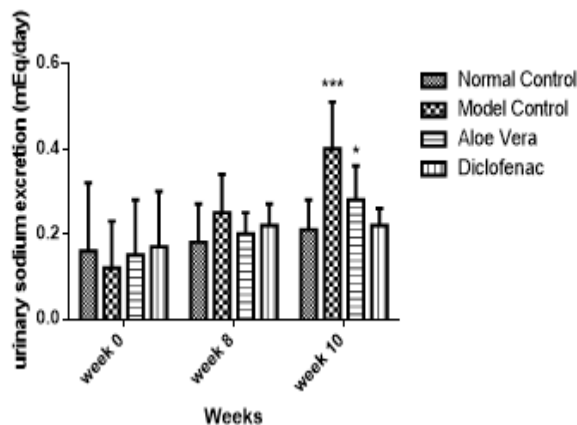


Figure 3: Effect of Aloe vera gel and diclofenac on urinary sodium excretion (Mean±SD) of hypertensive rats (n=6) Significance between groups calculated by Tukey's test.

*** p value <0.001 Versus Normal Control (A) & Diclofenac Group (D)

* p value <0.01 Versus Model control Group (B)

Discussion

Nonsteroidal anti-inflammatory drugs like diclofenac are the most commonly used and prescribed drug in our society. NSAIDs are being prescribed in our routine medical practice as analgesics, antipyretics and anti-inflammatory agents.²The pharmacological effects of NSAIDs on body organs depend upon the concentration and the time-duration of their use. The most affected organ is kidney, and therefore high doses or prolonged treatment can increase morbidity, especially in geriatric patients, as they already have declined renal functions. Moreover, these drugs disturb the normal electrolyte balance and affect the response of some diuretics which is expressed

as chronic retention of sodium and potassium. According to Aljadheyet *al.*, NSAID use is linked with a small increase in systolic blood pressure in hypertensive patients.¹²

The role of *Aloe vera* gel as an anti-inflammatory agent is well established. *Aloe vera* controls inflammatory reactions through different mechanisms. One of these mechanisms is closely associated with NSAIDs, i.e., inhibition of arachidonic acid pathway.¹³ This study was designed with an objective to compare the effects of *Aloe vera* gel and diclofenac on electrolyte balance in a hypertensive rat model. For this purpose, 20% sucrose diet was given to the rats, which successfully induced hypertension within the desired period of eight weeks. The results of this study clearly indicate that *Aloe vera* causes potassium loss paradoxical to the effect of diclofenac which causes potassium retention. Furthermore, it causes less sodium retention than diclofenac.

Diclofenac increases serum potassium concentration, possibly by inhibiting prostaglandin synthesis, resulting in decreased renin secretion, which reduces the level of aldosterone in the blood.¹⁴ Another mechanism of elevated serum potassium could be decreased synthesis of PGI₂ which stimulates renal juxtaglomerular cells to release renin and consequently aldosterone. The inhibition of PGI₂ by NSAIDs also causes decreased distal renal tubular flow and hyperkalemia.² An increase in the model control group may be linked to decreased sodium reabsorption as compensatory mechanism leading to increased potassium reabsorption in exchange. *Aloe vera* group exhibited a significant decrease in serum potassium from 8-10 weeks. Saka *et al.* expressed an insignificant decrease in serum potassium level when *Aloe vera* was given to healthy rats for 28 days,¹⁵ while higher dose, i.e., 800 mg/ Kg of chloroform extract of *Aloe vera* gel, significantly decreased serum potassium in healthy rats.¹⁶ This decrease in serum potassium may be an

aldosterone-like effect of *Aloe vera* gel sterols. Contrary to these results, six weeks of treatment with 600 mg/Kg dose of *Aloe vera* gel has shown to produce no change in serum potassium of normal rats and increase in serum potassium of salt-loaded rats,¹⁷ which was considered to be due to increased exchange with sodium.

The Present research shows an insignificant decrease in serum sodium level of diclofenac group during 8-10-week period. Another study has shown similar results in which 15 mg/kg dose of diclofenac given for five days did not produce any significant change in serum sodium concentration of Wistar rats.¹⁸ Serum sodium level of *Aloe vera* group showed a non-significant rise which is supported by another study in which chloroform extract of *Aloe vera* has shown an insignificant rise in serum sodium after 14 days of treatment which became significant after 28 days.¹⁹ Saka *et al.* showed the opposite effects of *Aloe vera* extract, which significantly decreased serum sodium concentration when given for 28 days.¹⁵ These studies were performed on healthy rats; no study is available for effect of *Aloe vera* on hypertensive rats.

Urinary sodium concentration and 24-hour excretion increased in all groups during the 8-10-week period, but this increase was significant only in the model control group and numerically negligible in the diclofenac group. At 10th-week, urinary sodium concentration and excretion were significantly higher in the model control group than all other groups which seems to be a normal compensatory mechanism, which is blunted with diclofenac treatment due to inhibition of renal prostaglandins.²⁰ *Aloe vera* caused less blunting of this compensatory mechanism. The reason may be lesser inhibition of prostaglandins by *Aloe vera* as compared to diclofenac which acts mainly by inhibition of COX, while the anti-inflammatory activity of *Aloe vera* is due to multiple mechanisms.²¹

The hematocrit of hypertensive groups decreased insignificantly from 8th to 10th week of the experiment, but this decrease was numerically more in diclofenac-treated rats. Aycan *et al.* made the same observation when forty male *Wistar* rats were treated with diclofenac (9mg/kg) intravenously, daily for five days.²² Sodium and fluid retention by diclofenac may be the reason for hematocrit decrease. *Aloe vera* did not affect hematocrit significantly in this study; Obeten *et al.* reinforced these effects of *Aloe vera* on hematology of *Wistar* rats.²³

To sum up the results, serum potassium was significantly higher in diclofenac group and significantly lower in *Aloe vera* group. Moreover, there was more decline in urinary sodium concentration and excretion with diclofenac than with *Aloe vera*, although difference between the two was statistically insignificant. So ultimately these parameters show that diclofenac has the tendency to cause more salt and water retention than *Aloe vera*. This is one of few studies on the effect of *Aloe vera* on electrolyte balance and first one on hypertensive rats.

The study has limitations that doses of *Aloe vera* gel and diclofenac were selected from two different studies. The anti-inflammatory effect of these doses was not compared in the present research. One would have been more confident in declaring *Aloe vera* a better anti-inflammatory option; had it been done. Administration of experimental drugs for two weeks is a short duration and another limitation. Long-term use of *Aloe vera* may reveal more sodium retention, or further lowering of serum potassium may be more harmful than sodium retention. Examination of histological effects may give a more clear picture.

Conclusion

Aloe vera causes less sodium retention than diclofenac but decreases serum potassium contrary to the effect of diclofenac in hypertensive rats. No

significant effect on hematocrit was seen. Further studies with different doses of *Aloe vera* and longer duration of intervention, as well as interaction with drugs, need to be conducted.

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Disclaimer

Current manuscript is part of the MPhil thesis research

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