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A STUDY ON NEPHROPROTECTIVE EFFECT OF AQUEOUS EXTRACT OF *PSIDIUM GUAJAVA* ON GENTAMICIN INDUCED NEPHROTOXICITY IN EXPERIMENTAL ANIMALS

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Keywords:

Psidium guajava, Gentamicin, Rats, Nephrotoxicity, Nephroprotective

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ABSTRACT: Objective: To evaluate the nephroprotective effect of aqueous extract of *Psidium guajava* leaves in gentamicin induced nephrotoxicity in albino rats. **Methods:** Adult albino rats were divided into 5 groups of 5 animal each, group I (normal control) treated with 2% Gum acacia orally, group II (positive control) treated with 2% Gum acacia orally with 100 mg/kg intraperitoneal gentamicin, group III (standard treatment) treated with silymarin (100 mg/kg b.w, orally) with 100mg/kg intraperitoneal gentamicin and groups IV–V (test groups) treated with aqueous extract of *Psidium guajava* leaves (AELPG) orally at doses of 200 and 300 mg/kg b.w with 100mg/kg intraperitoneal gentamicin respectively for 15 days. Serum Urea, S. Creatinine, S. Sodium, S. Potassium and S. Chloride analysis and microscopic examination of kidney were performed. **Results:** Gentamicin treatment caused nephrotoxicity as evidenced by significant elevation in serum urea, creatinine and electrolytes level respectively when compared to the normal control groups. Co-administration aqueous leaf extract of *Psidium guajava* with gentamicin significantly decreased the rise in these parameters in dose dependent manner. Similarly, silymarin treated group also significantly mitigated the biochemical markers of renal injury. Histopathological analyses revealed renal cell degeneration, necrosis, and inflammatory cell infiltration in gentamicin treated rats, whereas AELPG- and silymarin-treated groups mitigated the severity of gentamicin-induced renal damage. **Conclusion:** The study highlighted the protective role of *Psidium guajava* against renal injury induced by gentamicin thereby scientifically justifying its traditional use.

INTRODUCTION: Acute kidney injury (AKI) is a common clinical syndrome characterized by a sudden decline in or loss of kidney function. Acute tubular necrosis, caused by either ischemia or nephrotoxicity, is common setting in AKI [1].

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It is mainly can be caused by sepsis, ischemia-reperfusion, or nephrotoxic drugs [2]. The prevalence of kidney diseases is continuing to increase, currently there are approximately 850 million people having some kinds of kidney disorders worldwide.

Gentamicin-induced AKI is considered as a promising model to study the clinical effects of aminoglycosides on kidney [3]. It was the third systemically administered aminoglycoside antibiotic to be introduced for clinical use, and was obtained from *Micromonospora purpurea* in 1964

[4]. The toxicity of aminoglycosides, including gentamicin, is believed to be related to the generation of reactive oxygen species in the kidney [5]. In the field of medical research, traditional medicine has developed as a captivating source for researchers exploring alternative methods to treat complicated medical conditions including diabetes, digestive system nervous system and kidney injuries [6]. Natural plant are used for various applications including primary health care, cultural and traditional practices due to their low cost and safety [7]. *Psidium guajava* is a notable medicinal plant with enormous pharmacological potential [8].

Guava leaf extract is rich in bioactive compounds, including phenolic acids, flavonoids, tannins, terpines, alkaloids etc. which are well known to treat various disease through powerful antioxidant, anti-inflammatory and anticancer effect [9]. In addition, the aqueous extract of leaves of *Psidium guajava* exhibited significant activity against cyclosporine A induced nephrotoxicity in animal models. Silymarin (milk thistle), a flavonolignan complex extracted from the seeds of Silybum marianum, found to be nephroprotective against drug induced nephrotoxicity models in rats [10].

However, scientific data regarding protective effects of guava leaves against gentamicin induced nephrotoxicity are limited. Therefore, the present study was designed to investigate the nephroprotective effect of aqueous extract of *Psidium guajava* against gentamicin induced nephrotoxicity in rats, with comparative evaluation against the standard nephroprotective agent, Silymarin.

MATERIALS AND METHOD: The experimental protocol employed in the present investigation was reviewed and approved by the Institutional Animal Ethics Committee of Regional Institute of Medical Sciences (RIMS), Imphal, in accordance with the guidelines of the Committee for the purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. (Registration no.1596/GO/a/12/CPCSEA).

The study was conducted in the Department of Pharmacology, JNIMS, Imphal, Manipur, in collaboration with the Department of Biochemistry and Pathology.

Collection and Identification of *Psidium guajava* Leaves: The fresh leaves of *Psidium guajava* were collected in the month of February 2023 from Imphal West District. The plant was identified and authenticated by Life Science department, Manipur University (Mrs. Yumnam Sanatombi, guest faculty). A plant sample was deposited at the laboratory herbarium and allocated with voucher no. 001380MUMP.

Preparation of Plant Extract: The aqueous extract of *Psidium guajava* leaves was obtained by modification of the extraction procedure described by Massoudi EL *et al* [11]. The leaves were cleaned with water and air dried in shade for several days. The shade dried leaves were powdered using a mixture grinder. The powdered material were soxhleted with roughly ten times its volume of distilled water. The water was then heated to boil and subjected to extraction for 3 hours. On evaporation of water from filtrate, a deep brown residue was obtained which was stored in porcelain jar at 4°C for further use. In this way, the procedure is repeated several times to yield 20 gm of the extract. The aqueous *Psidium guajava* extract obtained by this method was used as the study material in entire study.

The Experimental Animal Used in the Study: 25 (twenty five) healthy albino rats of either sex weighing 150 to 200 gm were recruited from animal house of JNIMS, Porompat, Imphal and housed in the departmental polypropylene cages for 10 days for acclimatization in the laboratory atmosphere. The rats were fed with standard laboratory diet and water *ad libitum*. 12 hours dark-light cycle was maintained. The animals were fasted for 18 hours prior to the experiment and care taken to avoid any coprophagy.

Acute Oral Toxicity Studies: Acute oral toxicity study for the test extract of *Psidium guajava* leaves were carried out using OECD/OCED guidelines 425 [12]. The extract was found to be safe and no mortality was observed up to a dose of 2000mg/kg body weight per oral after 14 days.

Experimental Design [13]: The experiment was carried out for the period of 15 days. For this purpose, twenty five healthy albino rats of either sex and weighing approximately 150-200 gm were

used. The extracts of *Psidium guajava* leaves and silymarin was suspended in 2% Gum acacia. Animals were weighed, recorded, numbered and randomly divided into 5 groups of 5 animals each as follows:

Animals	Treatment
Group I (Normal control):	2% Gum acacia orally.
Group II (Positive control):	100mg/kg Intraperitoneal gentamicin + 2% Gum acacia orally
Group III (Standard drug):	100mg/kg Intraperitoneal gentamicin + silymar in 200mg/kg orally
Group IV (treatment group):	100mg/kg Intraperitoneal gentamicin+ *AELPG-200mg/kg body weight orally
Group V (treatment group):	100mg/kg Intraperitoneal gentamicin+ *AELPG-300mg/kg body weight orally

*AELPG- Aqueous extract of leaves of *Psidium guajava* all these protocols were continued for 15 days.

On the next day, all the animals were taken group wise and the rats from each group were anaesthetized using ether. Blood was collected from each of them for assessing various biochemical parameters- (S. Urea, S. Creatinine, S. Sodium, S. Potassium and S. Chloride). After collection of blood, the animals were sacrificed by cervical dislocation to collect the liver tissue for histopathological examination.

RESULTS: The values were expressed in specific units for those parameters as mentioned in the tables. Results are expressed as Mean± SEM (standard error of mean) of five animals at a time from each group.

The statistical significance was analyzed by using one way ANOVA, followed by Tukey-Kramer multiple comparisions test to compare between the different groups. The significance in the test was expressed by F-ratio and P- values of <0.05 was considered significant.

TABLE 1: SERUM LEVEL OF UREA, CREATININE, SODIUM, POTASSIUM AND CHLORIDE IN ALL GROUPS (MEAN±SEM)

Groups	Urea	Creatinine	Sodium	Potassium	Chloride
I	38.8 ± 1.83	0.38 ± 0.04	140.0 ± 0.55	3.92 ± 0.04	101.0± 0.32
II	100.4 ± 1.78#	1.12 ± 0.09#	145.0 ± 0.45#	5.06 ± 0.18#	105.6 ± 0.24#
III	44.8 ± 0.37*	0.48 ± 0.04*	141.0 ± 0.63*	4.18 ± 0.08*	102.2 ± 0.37*
IV	61.4 ±0.81*@	0.70 ± 0.03*@	143.20±0.37*@	4.56 ±0.09*@	104.2±0.37*@
V	46.6 ± 1.44*	0.54 ± 0.02*	141.80±0.80*	4.40 ±0.07*@	103.4±0.40*@
Oneway ANOVA	F	331.38	35.71	11.37	76.78
	df	4, 20	4, 20	4, 20	4, 20
	p	<0.05	<0.05	<0.05	<0.05

#P < 0.05 when compared to the normal control group (Group I), *P < 0.05 when compared to the positive control group (Group II), @P < 0.05 when compared to the standard group (Group III).

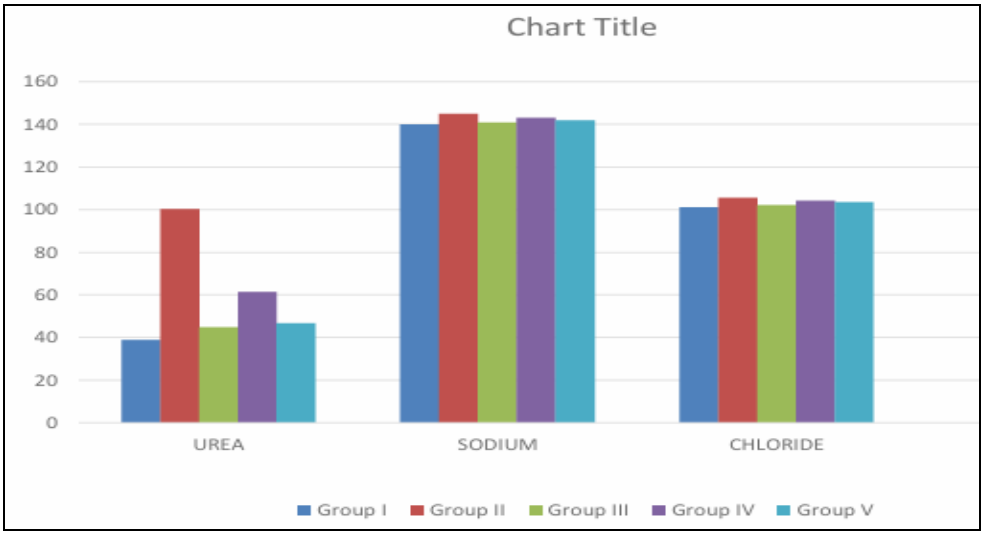

FIG. 1: BAR DIAGRAM SHOWING SERUM LEVELS OF UREA, SODIUM AND CHLORIDE IN ALL GROUPS. EACH VALUE IS EXPRESSED AS MEAN ± SEM

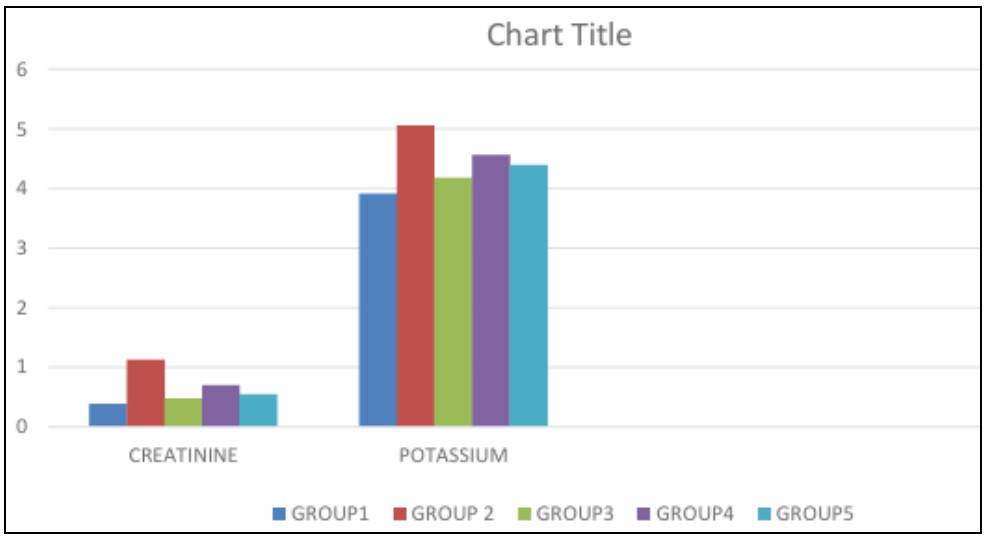

FIG. 2: BAR DIAGRAM SHOWING SERUM LEVELS OF CREATININE AND POTASSIUM IN ALL GROUPS. EACH VALUE IS EXPRESSED AS MEAN ± SEM

In the **Fig. 12** and **13**, group II which was given gentamicin to induce nephrotoxicity caused significant ($p< 0.05$) increase in urea (100.4±1.78), creatinine (1.12±0.09), sodium (145.0±0.45), potassium (5.06±0.18) and chloride (105.6±0.24) levels as compared to control group. In group III, which was treated with silymarin (200mg/kg) and gentamicin, when compared to group II showed a significant ($p<0.05$) decrease in serum urea (44.8±0.37), creatinine (0.48±0.04), sodium (141.0±0.63), potassium (4.18±0.08) and chloride (102.2±0.37) levels. Group IV which was treated with AEPGL at a dose of 200mg/kg causes a significant reduction ($p<0.05$) in the level of these parameters urea (61.4±0.81), creatinine (0.70±0.03), sodium (143.2±0.37), potassium (4.56±0.09) and chloride (104.2±0.37) as compared to group II and group III. Group V, AEPGL given at a dose of 300mg/kg showed a significant reduction ($p<0.05$) in the levels of urea (46.6±1.44), creatinine (0.54±0.02), sodium (141.8±0.80), potassium (4.40±0.07) and chloride (103.4±0.40) as compared to group II but when compared with group III, significant difference was found only in potassium and chloride levels. It is shown that there is significant dose-dependent reduction in serum urea, creatinine, sodium, potassium and chloride in the AEPGL treated groups as compared to positive control (group II).

Histopathological Findings:

Gross Features: The size, shape, colour contour and surface of kidney were normal without any significant changes in all the groups of animals of normal control, toxic control, silymarin treated and different doses of extract treated groups.

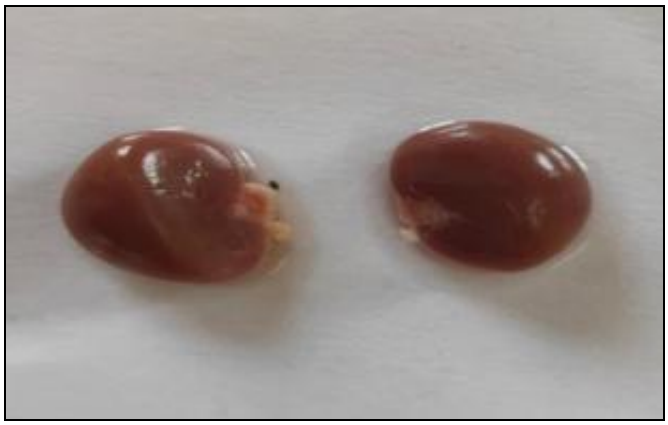

FIG. 3: GROSS KIDNEY SPECIMEN OF ALBINO RATS

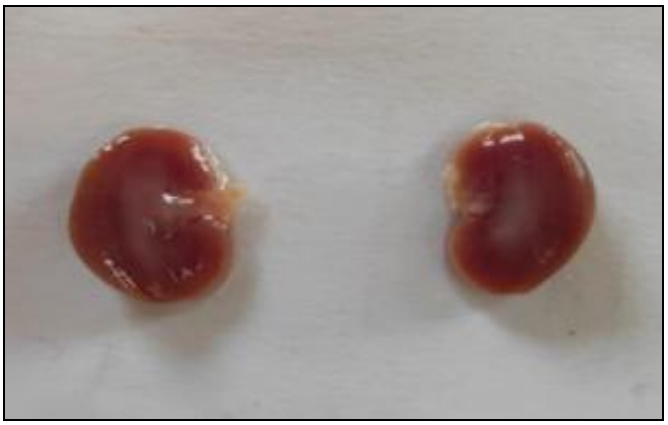

FIG. 4: DISSECTED KIDNEY OF ALBINO RATS

Microscopic Findings: In normal control group (group I), histology of the kidney exhibited normal tubule and glomeruli (Fig). Whereas in gentamicin induced group (group II) showed acute tubular

necrosis, degeneration of the proximal tubular epithelial cells and presence of slough in the lumen. Gentamicin induced inflammation of the renal interstitium. The silymarin (200mg/kg dose) treated group (group III) showed few tubules with degenerated epithelial cells and absence of interstitium. Group IV showed mild degeneration of proximal tubular epithelial cells with attenuation of the inflammatory cells group V, showed complete resolution of acute tubular necrosis and interstitial nephritis. All these findings indicate that the AEPGL have nephroprotective role when treatment was given with the extracts and gentamicin to the rats.

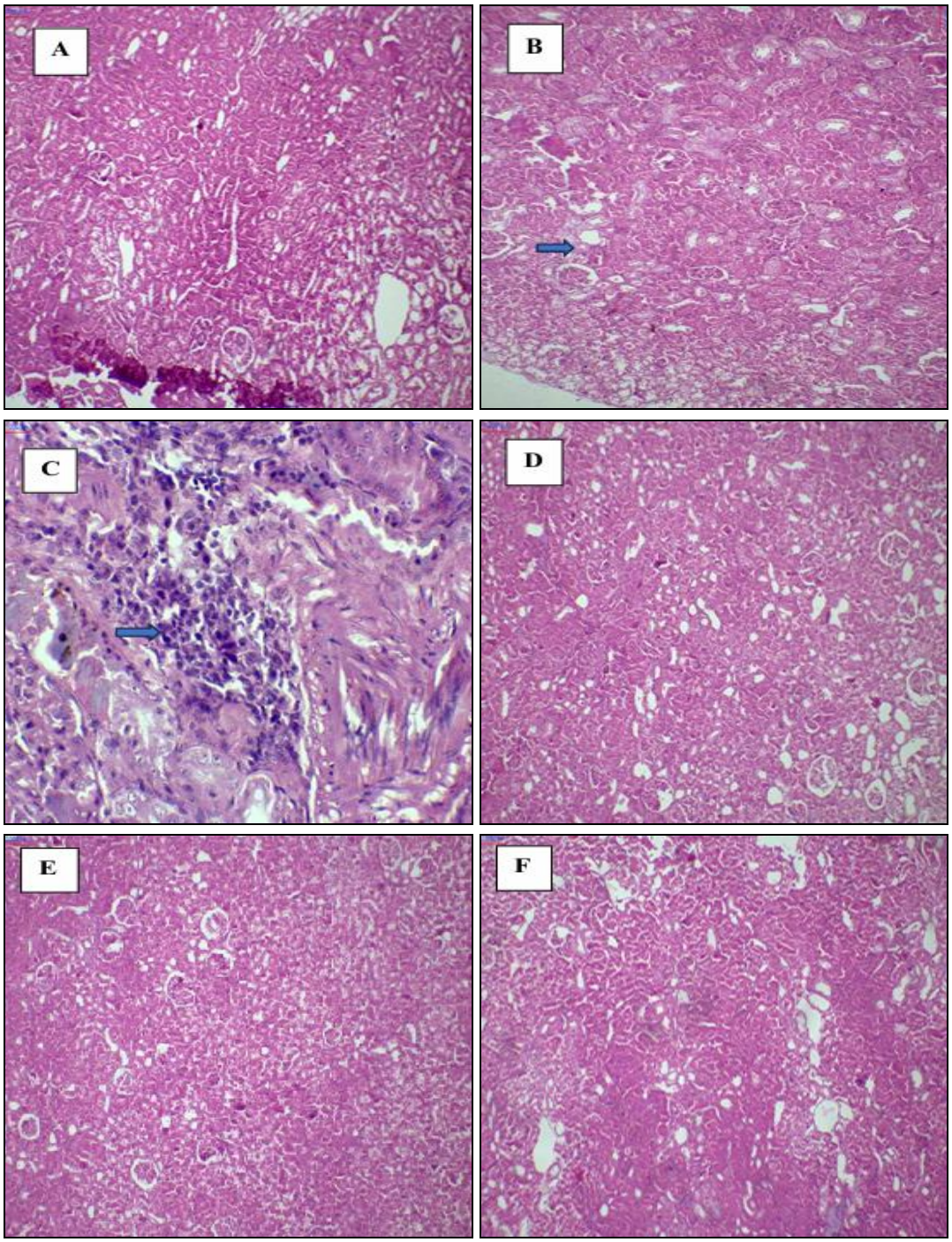

FIG. 5: HISTOPATHOLOGY OF RAT KIDNEY, H&E (A) NORMAL CONTROL, (B) & (C) POSITIVE CONTROL: SHOWED NECROSIS WITH DEGENERATION OF TUBULAR CELLS, INFLAMMATION OF INTERSTITIUM (D) STANDARD DRUG: GENTAMICIN (100MG/KG B.W. I.P) + SILYMARIN (200MG/KG B.W) SHOWED MARKED REDUCTION OF INFLAMMATION WITH FEW TUBULAR DEGENERATED CELLS (E), (F) TREATED WITH AEPGL 200 & 300MG/KG B.W + GENTAMICIN (100 MG/KG B.W I.P) SHOWED IMPROVEMENT IN NECROSIS WITH ATTENUATION OF INFLAMMATORY CELLS

DISCUSSION: Kidneys assume a pivotal role as primary targets susceptible to toxicity induced by chemicals owing to their integral involvement in the removal of harmful substances and their by products. Numerous therapeutic agents have been documented for their tendency to cause nephrotoxicity during clinical usage [14]. Phytocomponents such as phenolic compounds and flavonoids which are generally available in plants are responsible for antioxidant properties and have nephroprotective properties. This makes medicinal plants a great potential source for pharmaceutical products [15]. In previous study, the leave extract of guava has nephroprotective, antidiabetic, anticancer, anti-inflammatory and antioxidant property [7]. There is less evidence regarding the nephroprotective effect of AEPGL against gentamicin induced nephrotoxicity in rats.

Gentamicin a frequently prescribed aminoglycoside antibiotic, is widely recognised as a significant contributor to drug-induced kidney damage. Gentamicin accrues within the renal tubular cells, disrupting cellular functions and impairing the kidneys' ability to filter waste products and maintain electrolyte balance. It instigates the production of free radicals and mitochondrial dysfunction, culminating in cellular injury and apoptosis. Additionally, it disturbs the delicate balance of ions and transport mechanisms within the kidney, affecting its overall function [14].

In the present study, gentamicin at a dose 100mg/kg induced elevated levels of s. urea, creatinine and electrolyte imbalance in the untreated toxin group as compared to the normal group, corroborating findings depicted by Nikhil *et al* [16]. Gentamicin causes acute tubular necrosis and reduces glomerular filtration by multiple processes such as blockage of nephron by necrotic epithelial debris, back leak of fluid into the interstitium, direct renal vascular constriction and activation of renin-angiotensin system leading to raised in serum urea and creatinine [17]. However, regarding serum sodium, potassium and chloride levels a nonsignificant increase was seen in gentamicin induced mice. The possible mechanism for elevated levels of these electrolytes have been described to the alteration of kidney function, or reduced glomerulation filtration rate and decreased reabsorption of water caused by gentamicin [18].

Rats treated with AEGPL at doses of 200 and 300 mg/kg prevents increase in s. urea, creatinine, Na^+, K^+, Cl^- induced by gentamicin in dose dependent manner. The protective action of aqueous extract of leaves of *Psidium guajava* is very promising as evidenced by the reversal of the altered values following administration of extracts probably by attenuation of oxidative stress-induced renal damage. The histopathological observation basically supported the result obtained from biochemical parameters of the study. Necrosis and inflammation induced by gentamicin was prevented by treatment with AEPGL at 200 and 300mg/kg doses. It is evident from the histological findings that there were attenuation of inflammatory cells and resolution of necrosis in the groups treated with AEPGL at 200 and 300mg/kg doses.

Antioxidant such as flavonoids, glycosides, steroids, tannins, and saponins has the potential to improve kidney function [19]. Flavonoids, polyphenolic compounds such as ferulic caid, catechin, gallic acid, rutin quercetin, vanillic acid reduced the nephrotoxicity of gentamicin via the increase in antioxidant enzymatic activity, decrease the lipid peroxidation, scavenge the free radicals and improve the tissue architecture of the kidneys [20]. Manoj K *et al* [21] revealed aqueous extract of *Psidium guajava* leaves for presence of phenolic acids, flavonoids, glycosides, saponins and phenolic compounds such as quercetin, gallic acid, catechin, epicatechin, chlorogenic acid, caffeic acid and kaempferol. The possible mechanism of nephroprotective activity may be due to the protective action of the natural antioxidant present in the aqueous extract of the leaves of *Psidium guajava* and renal cell protection as depicted by histopathological findings. Since phytochemicals present in AEPGL includes compounds like tannins, flavonoids, saponins, phenolic compounds which are natural antioxidants and may be involved in the nephroprotective activity. Thus, the findings of the current study strongly suggest that the nephroprotective activity of *Psidium guajava* is mediated through antioxidant properties and its ability to protect renal cells injury, as evidenced both biochemically and histologically.

CONCLUSION: The present study showed that the aqueous extract of the leaves of *Psidium guajava* has significant nephroprotective action

against gentamicin induced nephrotoxicity in albino rats. The nephroprotective activity of *Psidium guajava* may be due to the presence of bioactive compounds like flavonoid, saponin, tannin, alkaloid and phenolic compounds. These compounds increase the antioxidant enzymatic activity and scavenge free radicals and improve the tissue architecture of the kidney. These could be the mechanism of nephroprotective activity of *Psidium guajava*. The study indicates that the aqueous extract of *Psidium guajava* may be used as an effective nephroprotective agent. Further research with more purified form of extract is necessary to gain a better understanding of its mechanism of actions at cellular and molecular levels, safety and efficacy of the active ingredients of the plant extract and to establish it as a potential nephroprotective drug in near future.

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