Volume 3, Issue 8, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

EVALUATION OF NEPHROPROTECTIVE POTENTIAL OF SELECTED SCHIFF BASES (SW8/SB & SW10/SB) AGAINST GENTAMICIN-INDUCED NEPHROTOXICITY

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DOI: https://doi.org/10.5281/zenodo.17423546

Keywords
Gentamicin, Schiff bases, Kidney, S. Creatinine, Blood Urea Nitrogen (BUN), Nephrotic diseases, nephroprotection.

Article History
Received: 01 September 2025
Accepted: 12 October 2025
Published: 23 October 2025

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Abstract

The kidneys are essential organs that conduct a wide range vital functions in the body just like preserving homeostasis, detoxification of the toxic materials and controlling the internal environment of the body. Worldwide, nephropathy has been reported in many countries, regardless of age, and gender. Nephrotoxicity arises when the kidneys are continuously exposed to xenobiotic such as alcohol, drugs, poisons and other toxic chemicals. Although the kidneys are responsible for most drugs detoxification, still numerous medicines cause infections in kidney. In these halothane, amoxicillin, minocycline and gentamicin etc drugs are included. The specific mechanism of causing nephrotoxicity by these drugs are yet unknown but some hypothesis suggested they can generate free radicals which can cause injury in particular organ of the body. In this advance era of drugs discovery, there is no drugs available that completely protect the kidneys from nephrotoxicity. Schiff bases are chemical compounds with a wide range of biological consequences, including cytotoxic, antioxidant and anti-inflammatory capabilities. The current study focuses on the nephroprotective potential of various Schiff base dose against nephrotoxicity caused by gentamicin in an animal model. Gentamicin 100 mg/kg was administrated as part of the study to cause nephrotoxicity, and the mice are subsequently given various dosages of Schiff bases (CA 25 mg/kg & 50 mg/kg and CB 25 & 50 mg/kg) for eight days. Serum creatinine and BUN, two nephrotic indicators were checked out to determine kidney function. Additionally, histopathological analyses were conducted to evaluate nephrotic disorders. Treatment with gentamicin increased Serum creatinine and BUN levels, indicating cause of nephrotoxicity. These nephrotic indicators were decreased after Schiff base treatment. In addition, renal tissue under gentamicin administration had histopathological changes that included polycystic kidney disease (PKD, hydropic dilatation and pyknotic nuclei. Histopathological changes were reduced nearly normal after treatment with Schiff bases. As a result of study,

Volume 3, Issue 8, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Schiff bases were found to reduce gentamicin-induced biomarkers of nephrotic dysfunction and reverse histopathological changes caused by gentamicin. Furthermore, Schiff bases may have nephroprotective effects due to their antioxidant properties.

INTRODUCTION

Almost 20-25% of body's blood circulation is received by kidneys, which enables it to properly dispose of metabolic wastes. In this way kidneys play important role in regulating body's homeostasis [1]. In addition to toxins, kidneys also eliminate drug substances from body. That's why abnormal function of kidneys pose body to many health issues [2]. Worldwide including Pakistan, the spreading of kidney diseases become a public health issue [3]. According to some studies, about more than 10% of people worldwide suffering from chronic renal illness [4]. In 2016, kidney disease was identified as the 16th leading cause of mortality and it is expected to rise to the 5th position by 2040 [5]. Among diseases related to kidney, kidney tumor, cysts formation and nephrolithiasis (kidney stone) are the three most prevalent diseases that have an impact on kidney functions. According to research which was published in 2017 that estimated the overall number of kidney diseases related deaths worldwide from 1990 to 2017. The survey stated that, on average, more than 13 million people globally died each year. The research also revealed that there were approximately over 10 million deaths in 2017. It represented about 17 % of all deaths during that year [6]. The clinical syndromes that can be recognized in drug-induced nephropathy are acute renal failure, chronic interstitial nephritis and nephrotic syndrome. Four important causal agents of acute tubular necrosis are aminoglycosides, amphotericin B, radiocontrast agents and cyclosporin. Approximately half of the cases of drug-induced renal failure are related to the use of aminoglycosides. The aminoglycosides are particularly nephrotoxic when combined with other nephrotoxic drugs [7]. Aminoglycoside antibiotics are employed clinically because of their potent bactericidal activities, less bacterial resistance, post-antibiotic effects and low cost. However, drugs belong to this class are well-known to cause nephrotoxicity, which limits their frequent clinical exploitation. Gentamicin, a commonly used aminoglycoside, is associated with an induction of tubular necrosis, epithelial edema of proximal tubules, cellular desquamation, tubular fibrosis, glomerular congestion, perivascular edema and inflammation, which ultimately leads to renal dysfunction. [8]. The kidney damage caused by gentamicin is intricate. The actual processes driving gentamicin-induced nephrotoxicity encompass alterations at the molecular and cellular levels, including oxidative stress, disruption of renal cell membranes, and reduction in renal blood flow [9].Schiff bases are derived chemical group from aldehydes or ketones in which the carbonyl group is interchanged by functional group (-C=N-) an imine or azomethine as shown in figure 1. In the Schiff base structure, the double bond between Nitrogen atom and Carbon atom allows the nitrogen atom to form a chemical bond with an aryl or alkyl group [10]. Hugo Schiff, a German scientist, in 1864 first described these chemicals, known as Schiff bases [11]. These bases have a variety of beneficial characteristics, such as anti-inflammatory [12], painkiller [13], anti-bacterial [14], anti-epileptic [15], anti-tuberculosis [16], cytotoxic [17], free radical scavenging [18], and antihelminthic [19]. In recent years, metal complexes of Schiff bases have become more important. When transition metals combine with Schiff bases, their biological activities change [20]. Schiff bases can be used as a corrosion inhibitor by creating a monolayer to protect damaged regions [21].

Due to limited data available on the nephroprotective effect of Schiff bases as well as significant anti-inflammatory and antioxidant activities of Schiff bases, that's why this research focuses on the nephroprotective effect of Schiff bases against gentamicin-induced nephrotoxicity.

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Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

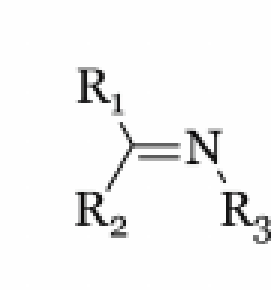

Figure 1. General structure of Schiff base, R Alkyl or Aryl group

2. Materials and methods

2.1 Preparation of Schiff Bases

Schiff bases synthesis is done in two phases. In first phase there is condensation of amine-containing aldehyde or ketones molecules to produce the intermediate product known as carbinolamine. The second phase involves dehydration of intermediate molecules. Dean Stalk apparatus is employed for this reaction. The reversible Schiff base reactions produce an intermediate molecule known as carbinolamine, which may be heated or dehydrated using an acid or basic catalyst. Molecular sieves are used to eliminate all water once the reaction is completed. Process completion is achieved by dehydration or removal of the final product [22].

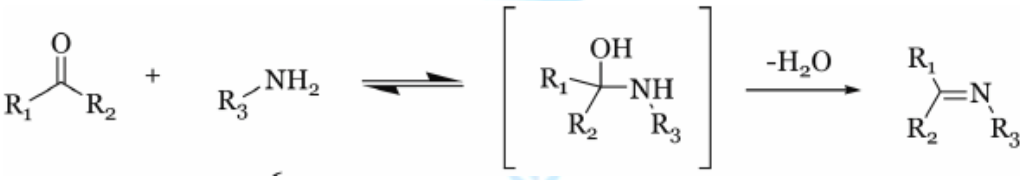

Figure 2. Reaction involved in Schiff base synthesis

2.2 Chemicals

- Gentamicin, silymarin (Manufactured by Abbott Laboratories, Pakistan) and normal saline (Manufactured by Marions Laboratories Pakistan) were purchased from Muhammad Zai medical store, Peshawar, Pakistan.
- 10% Neutral Buffered Formalin (Manufactured by Sigma-Aldrich, USA) and chloroform (Manufactured by Sigma Aldrich, USA) were supplied by the pharmaceutical chemistry lab of pharmacy department, AWKUM.
- Syed Wadood Ali Shah (Asst. Prof. University of Malakand, Pakistan) assisted in the synthesis of compounds (SW8/SB & SW10/SB). These compounds were dissolved in Di Methyl Sulphoxide (Manufactured by Akkshat Pure Chem, India) and in saline. Chemical structures of both compounds to be studied, SW8/SB & SW10/SB are illustrated in figure 3 & 4 respectively.

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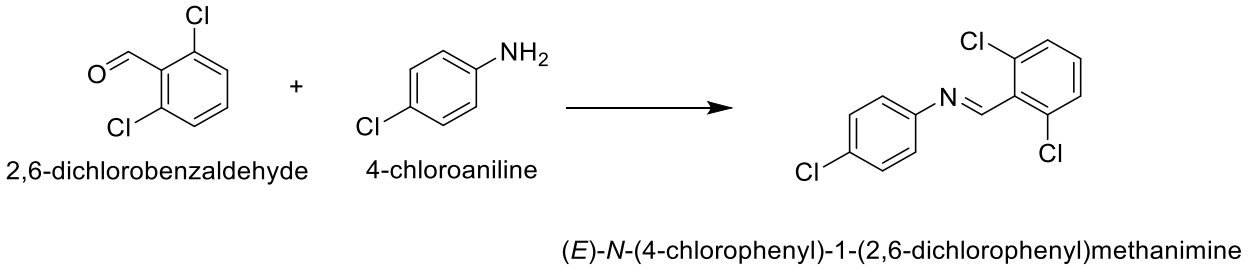

Figure 3. Chemical Structure of Schiff Base SW8/SB or Compound A (CA) or 2, 6-dichlorobenzaldehyde + 4-chloroaniline or (E)-N- (4-chlorophenyl)-1-(2, 6-dichlorophenyl) methanimine

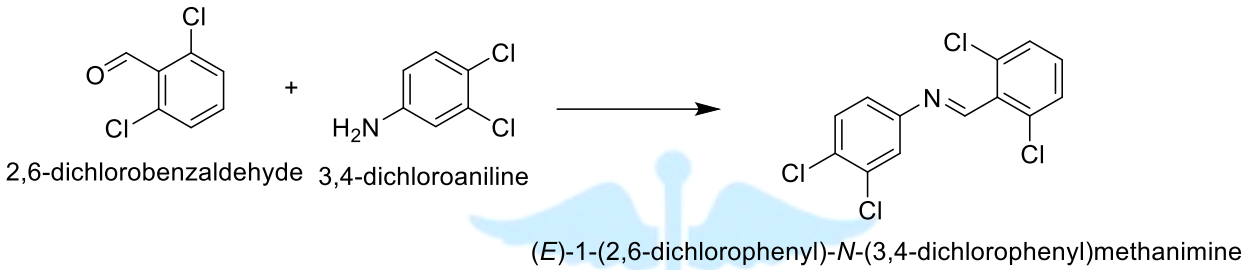

Figure 4. Chemical Structure of Schiff Base SW10/SB or Compound B (CB) or 2, 6-dichlorobenzaldehyde + 3, 4-dichloroaniline or (E)-1-(2, 6-dichlorophenyl)-N-(3, 4-dichlorophenyl) methanimine

2.3 Animal selection and protocol

In this research study, Swiss Albino mice of both gender weighing 25-35 gms were used as model animals. The model animals were kept in according to standard laboratory protocols which include controlled humidity and temperature (24±2°C), proper ventilation, proper food and water systems in control environment. The mice were acclimated seven days before experimentation. The procedure was carried out according to the standards imposed by the panel of experts from the department of pharmacy at Abdul Wali Khan University Mardan (AWKUM). Six groups of five experimental animals each were created out of the total thirty mice. All the experimental animals were treated with synthetic compounds and selected medicine for eight days, which are given below:

Group 1 Mice of this group were considered as a control group treated with normal saline only.

Group 2 The mice of this group were administrated 100 mg/kg/day gentamicin intraperitoneally (I.P.) to induce nephrotoxicity. Based on previous study, this nephrotoxic dose 100mg/kg/day of gentamicin was selected [23].

Group 3 This group received gentamicin (100 mg/kg/day) I.P. with the addition of Compound A (25 mg/kg/day) orally.

Group 4 This group received gentamicin (100mg/kg/day) I.P. along with Compound A (50mg/kg/day) orally.

Group 5 This group received gentamicin (100 mg/kg/day) I.P. and Compound B (25 mg/kg/day) orally.

Group 6 In addition to intraperitoneal administration of gentamicin (100 mg/kg/day), this group also got Compound B (50mg/kg/day) orally.

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Blood samples were taken on the ninth day, using the heart puncturing procedure. To study histopathological alteration, a portion of each animal's kidney was also separated and stored in 10% Neutral Buffered Formalin (NBF) [24].

2.4 Measurement of biochemical and evaluation of enzymatic activities

When the treatment period was completed, chloroform was used to anesthetize the selected animals. Through intracardiac puncture, blood samples were collected and then placed into gel tubes. After that, these tubes were incubated for 15 minutes at controlled temperature ranging from 20 to 25°C. Samples were then centrifuged for five minutes at 4000 rpm after the incubation period. Using a micropipette, the serum was carefully extracted from the gel tubes after centrifugation and placed into the eppendrof tubes. Then the serum were placed in refrigerator at 2-8°C for further analysis.

Consequently, the kidney's different biochemical tests were performed to check the kidney's function after exposure to drugs. In these tests, Serum Creatinine and Blood Urea Nitrogen (BUN) were specially focused. Serum creatinine and BUN values are the biomarkers used in the kidney function test [25]. Blood creatinine and BUN levels rise because of extensive damage to renal parenchymal cells [26]. It is believed that reactive oxygen molecules (ROS) are responsible for the kidney damage caused by gentamicin, as they cause tissue to deteriorate and degrade. Gentamicin's inhibition of antioxidant-producing enzymes in the renal mitochondria supports the ROS effect [27]. To perform these tests, different diagnostic kits and auto analyzers were used to measure and analyze kidney function properly. The results of these tests revealed insights on the Nephroprotective effects of the treatments on selected experimental animals [28].

2.5 Histopathological Preparations

In order to analyze histopathological alterations under light microscope, kidney tissues preserved in 10 % NBF were fixed in paraffin. Using microtome, 4-5 micrometer thick sections of each tissue were cut. Finally, hematoxylin and eosin were used to stain the tissue [29].

2.6 Statistical Interpretations

The findings were expressed in mean ± SEM and statistical significance were measured through one-way analysis of variance (ANOVA) using Graph Pad prism 5 software. The values for

- *$p<0.05$ were considered significant,
- **$p<0.01$ were considered more significant
- And ***$p<0.001$ were considered highly significant. [30].

3 Results

3.1 Characterization of kidney biomarkers

3.1.1 Serum Creatinine

As compared to control group, gentamicin-induced mice (GTN) exhibited a rise in serum creatinine level more significantly (***$p<0.001$). On the other hand, administration of Schiff bases at certain doses resulted in decrease in the level of serum creatinine as compared to gentamicin-induced mice. As shown in fig. 5, compound A (CA) at a dose level of 50mg/kg and compound B (CB) at a dose level of 25mg/kg and 50 mg/kg decreased the serum creatinine level more significantly as compared to gentamicin treated group (***$p<0.001$). No significant decrease/effect was found in the serum creatinine level in mice treated with compound A (CA) Schiff bases at a dose level of 25mg/kg.

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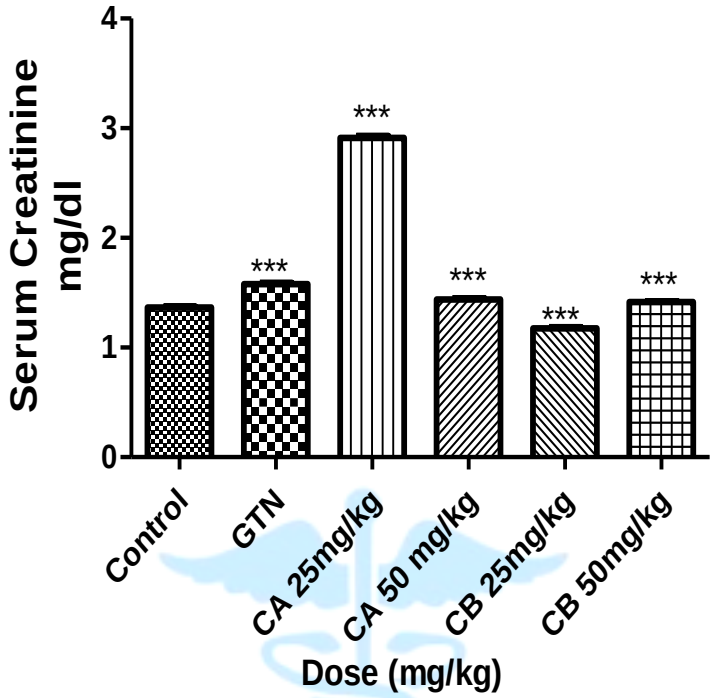

Figure 5. Graphical Representation of effects of gentamicin and different doses of Schiff bases on serum creatinine level.

3.1.2 Blood Urea Nitrogen (BUN)

Reference to fig. 6, increased level of BUN was found in gentamicin-induced mice as compared to control group (**p<0.01). However, administration of compound A (CA) and compound B (CB) resulted in decrease in the level of BUN as compared to gentamicin-induced mice. Compound A (CA) at a dose level of 25mg/kg and both doses (25mg/kg and 50mg/kg) of compound B (CB) decreased the BUN highly significantly (***p<0.001) as compared to gentamicin-induced mice. However, compound A (CA) at a dose level of 50mg/kg reduced the BUN more significantly (**p<0.01).

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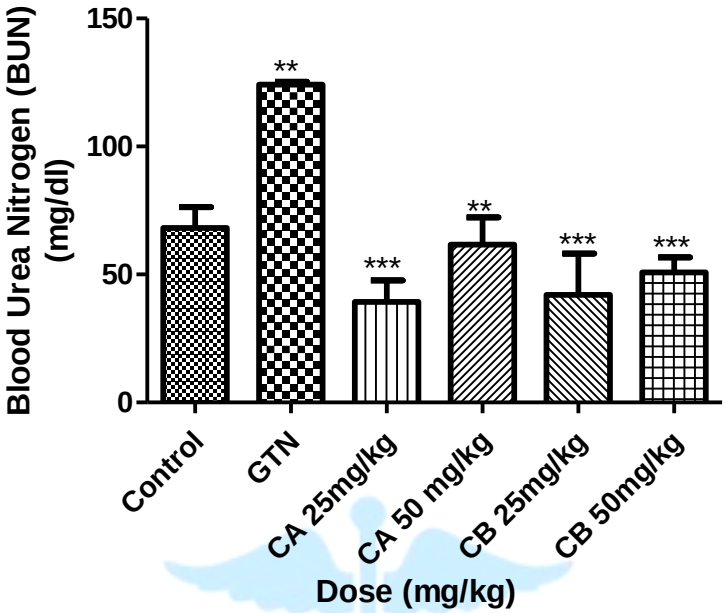

Figure 6. Graphical Representation of effects of gentamicin and different doses of Schiff bases on blood urea nitrogen.

3.2 Histopathology of kidneys

According to histopathological findings, almost normal histoarchitecture of kidney of group treated with normal saline (control) was found characterized by well-defined structures of glomerulus, bowman's capsule, proximal convoluted tubules and distal convoluted tubules as shown in figure 7.

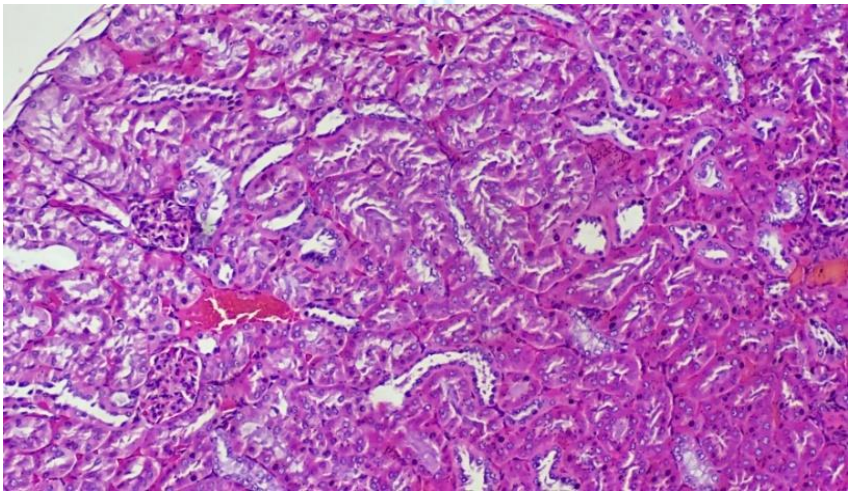

Figure 7: Photomicrograph of control group

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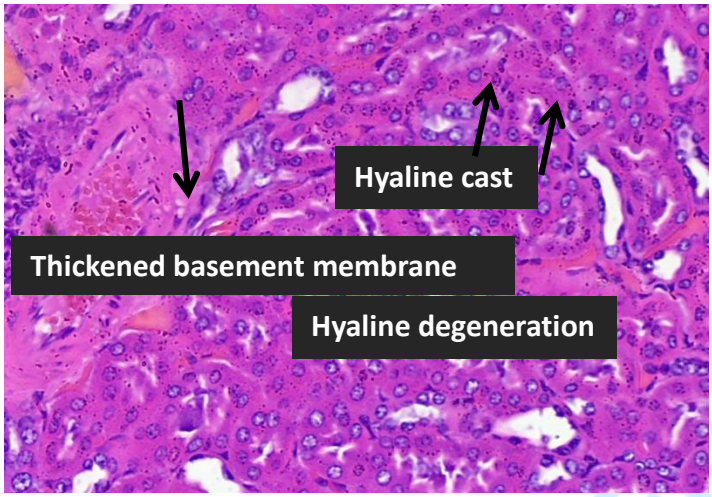
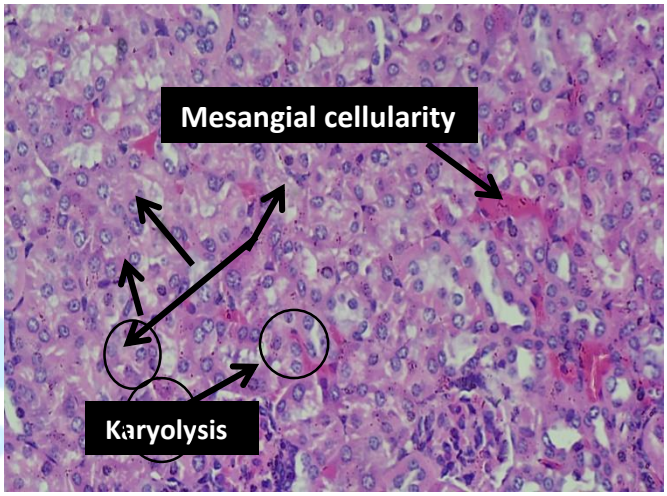
However, gentamicin-induced group exhibited different pathological alterations in kidney such as mesangial cellularity, karyolysis, hyaline cast, hyaline degeneration, thick basement membrane, perivascular interstitial inflammation, eosinophilic hyaline cast and degenerative changes in tubules as compared to control group (figure 8).





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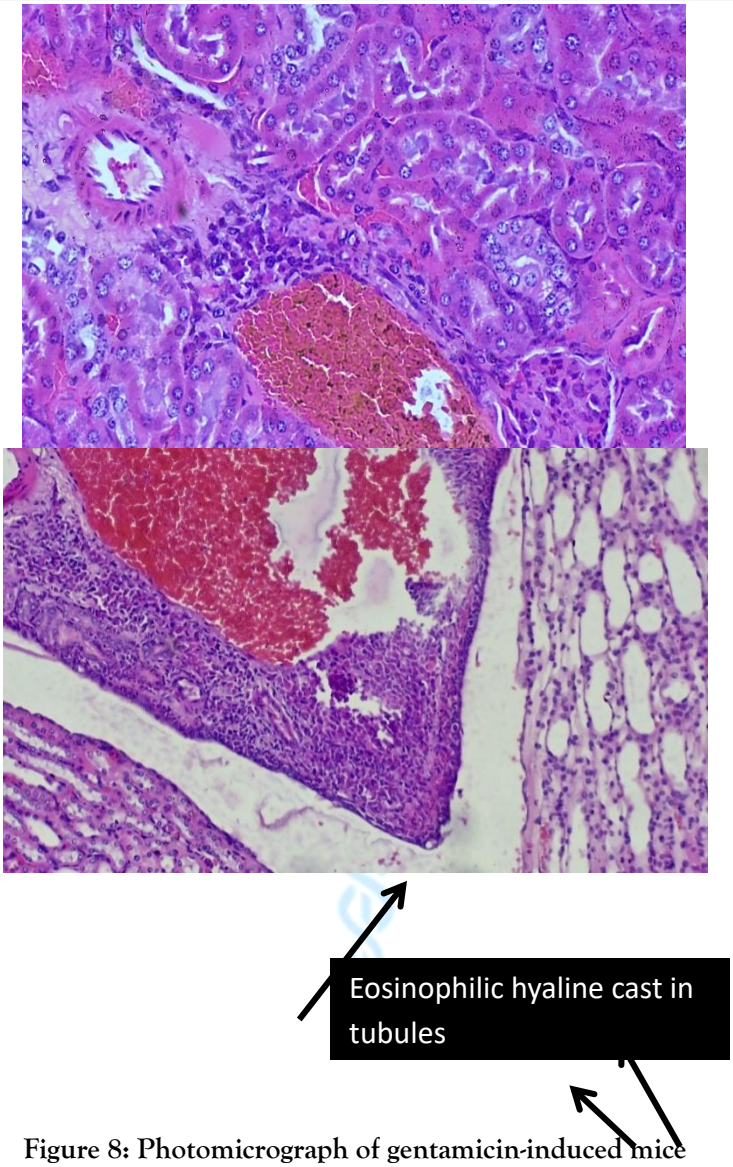
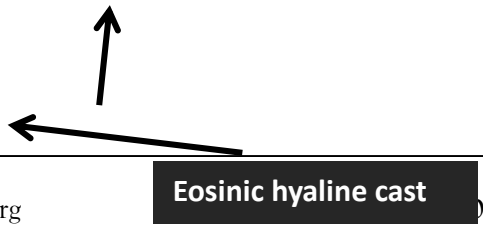


Figure 8: Photomicrograph of gentamicin-induced mice

On the other hand administration of Schiff bases at certain doses returned these pathological changes to almost normal histoarchitecture. Group treated with compound A (CA) at a dose level of 25mg/kg showed little pathological changes. Changes such as congested blood vessels and chronic inflammatory infiltrate have been found in this group (figure 9).



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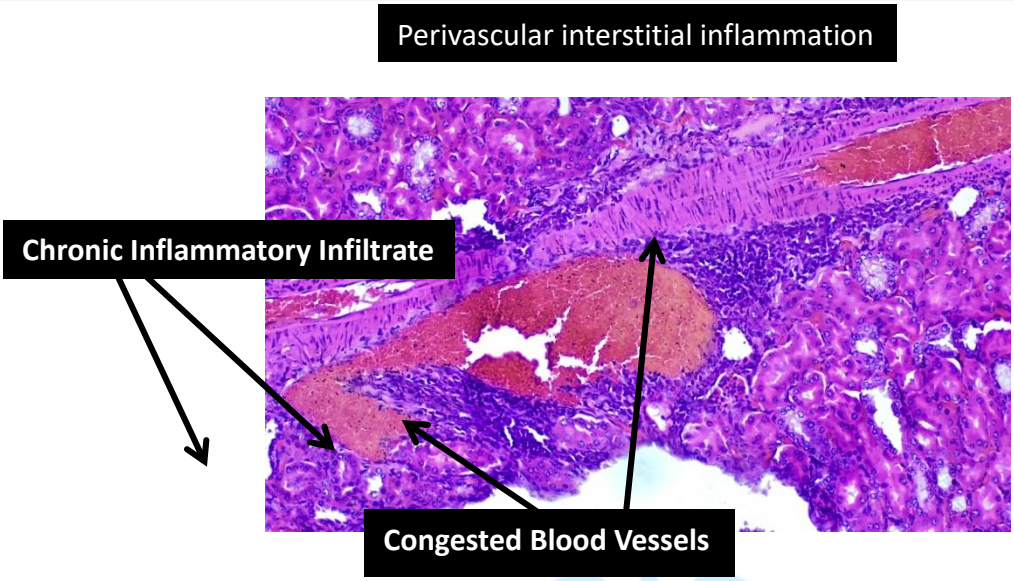
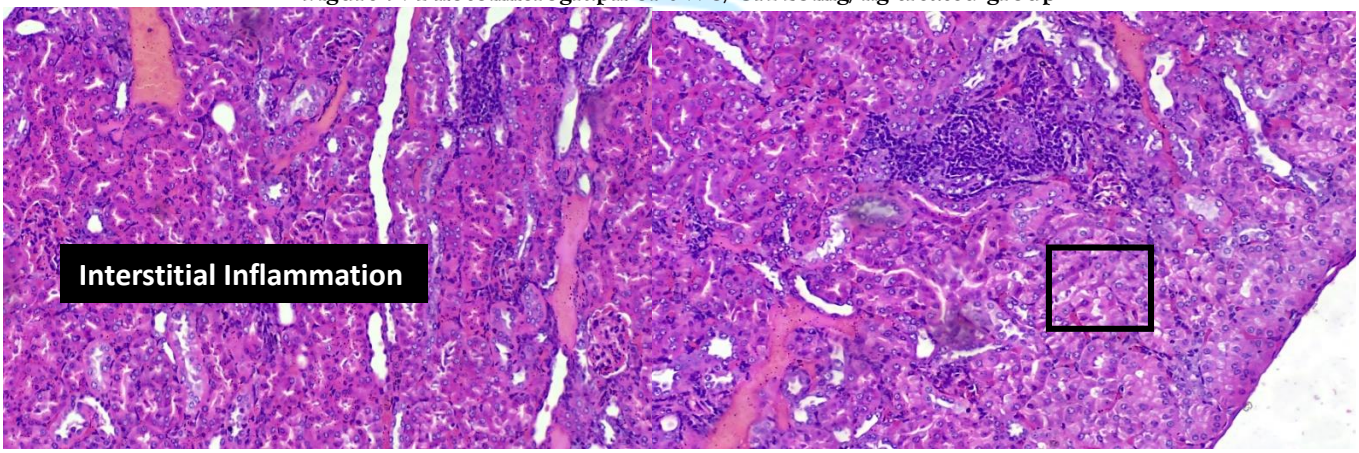


Figure 9: Photomicrograph of SW8/CA 25mg/kg treated group



Group treated with compound A (CA) at a dose level of 50mg/kg relieved these pathological changes to a greater extent with few changes still present. Moreover, this group has been found with normal glomerulus (figure 10).

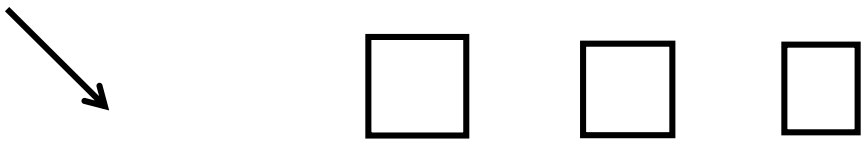


Figure 10: Photomicrograph of SW8/CA 50mg/kg treated group (: Normal glomeruli)

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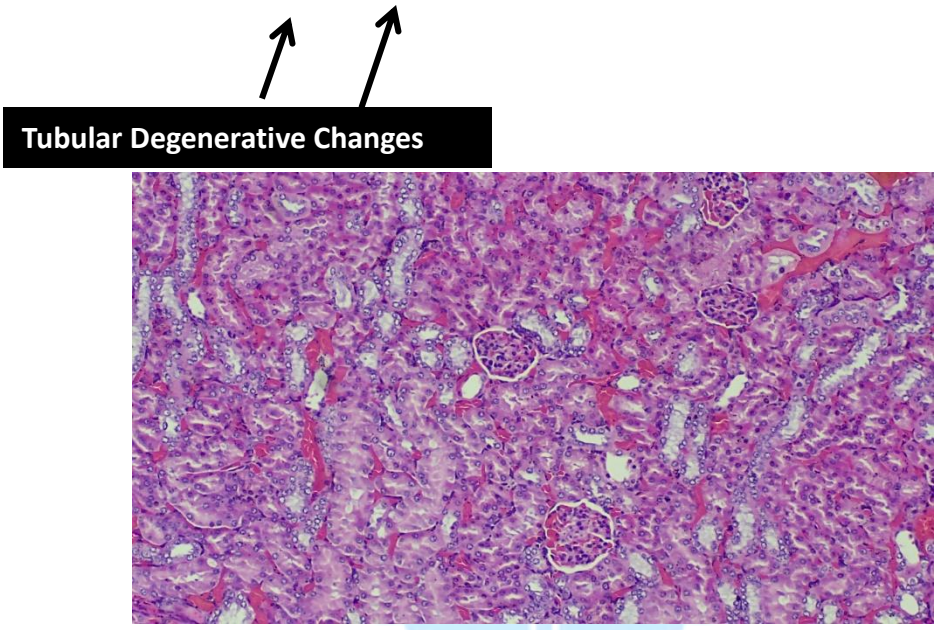

Similarly, group treated with compound B (CB) at a dose level of 25mg/kg exhibited less degenerative changes in tubules, minimal inflammation and normal glomeruli (figure 11).

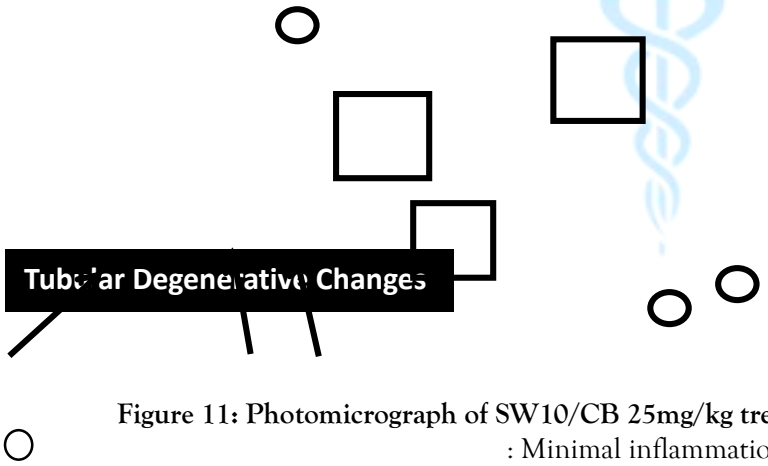

Figure 11: Photomicrograph of SW10/CB 25mg/kg treated group (: Normal glomeruli, : Minimal inflammation)

Group treated with compound B (CB) at a dose level of 50mg/kg showed less inflammation, less tubular degeneration, less tubular dilatation and normal glomeruli (figure 12).

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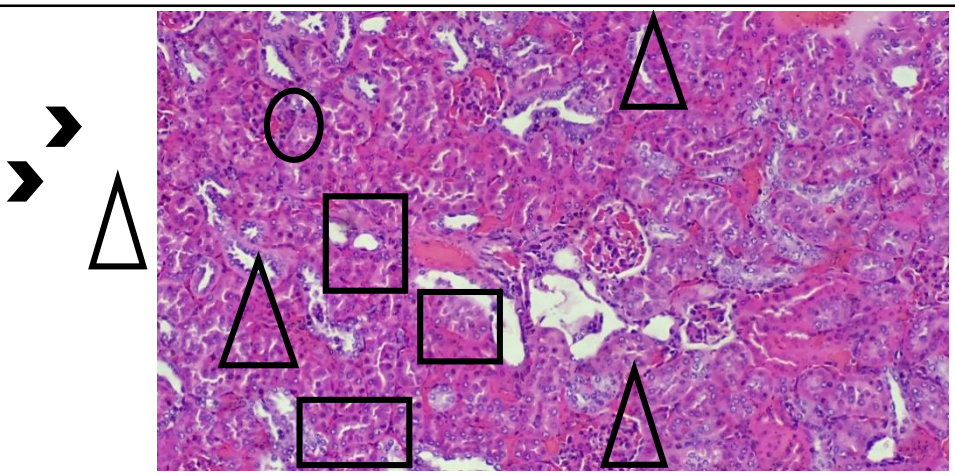

Figure 12: Photomicrograph of SW10/CB 50mg/kg treated group (: Normal glomeruli :○ Less Inflammation, △ : Less tubular dilatation, ❯ : Less tubular degeneration)

4 Discussion:

The current study provides evidence of the nephrotoxic effect of gentamicin characterized by increased levels of serum creatinine and BUN, supporting earlier findings [31]. The rise in BUN and serum creatinine levels in gentamicin-induced mice highlights the drug's ability to harm renal function through tubular damage and oxidative stress [32].

It is interesting to note that the administration of Schiff bases, especially compound B (CB), evinced a nephroprotective effect by alleviating the rise in serum creatinine levels. At dose levels of 25 mg/kg and 50 mg/kg, CB reduced serum creatinine levels compared to the gentamicin-treated group, supporting its ability to protect against gentamicin-induced nephrotoxicity. These findings are consistent with studies representing antioxidant and nephroprotective properties to Schiff bases. However, compound A (CA) failed to elicit a significant reduction in serum creatinine levels, indicating possible variations in efficacy based on the structural or pharmacodynamic properties of these compounds.

Similarly in case of BUN level, gentamicin-induced mice exhibited a marked increase in BUN levels, consistent with renal impairment. Administration of both CA and CB reduced BUN levels in gentamicin-induced mice. These results suggest a potential nephroprotective trend. The inability of Compound A to significantly alter serum creatinine levels further emphasizes the need for structural modifications or combined therapies to enhance its efficacy.

The histopathological studies furthure supported the nephroprotective ability of Schiff bases. Well-defined glomeruli, Bowman's capsules, and tubular structures, consistent with normal kidney physiology have been found in renal histoarchitecture of control group. In contrast, the gentamicin-treated group represented severe histopathological alterations characterized by mesangial cellularity, karyolysis, hyaline degeneration, thickened basement membranes, interstitial inflammation, and tubular degeneration. These findings are in agreement with previous reports that gentamicin causes nephrotoxicity primarily by generating reactive oxygen species (ROS), lipid peroxidation, and inducing tubular necrosis.

Administration of Schiff bases markedly relieved these histopathological abnormalities in a dose-dependent manner. Treatment with compound A at 25 mg/kg showed partial protection with mild vascular congestion

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and chronic inflammatory infiltrates, while at 50 mg/kg, compound A effectively restored renal histoarchitecture with only minimal residual alterations, suggesting improved nephroprotection at higher doses. Similarly, compound B at 25 mg/kg reduced degenerative tubular changes and inflammation, while 50 mg/kg provided substantial protection with normal glomeruli and minimal inflammation, indicating a stronger nephroprotective effect at the higher dose.

The improved histoarchitecture in Schiff base–induced groups may be attributed to their antioxidant and free radical scavenging properties, which likely reduce oxidative stress–stimulated renal injury. Schiff bases have been reported to possess anti-inflammatory and cytoprotective activities, which could explain the reduced tubular degeneration, inflammation, and preservation of glomerular structure observed in this study.

Overall, both Schiff base compounds demonstrated significant nephroprotective activity, with higher doses providing more effective protection against gentamicin-induced renal damage. The nephroprotective potential may be due to inhibition of oxidative stress, stabilization of cellular membranes, and modulation of inflammatory responses.

Conclusion

The observed nephroprotection may be attributed to the antioxidant, anti-inflammatory, and cytoprotective properties of Schiff bases, which likely alleviate oxidative stress and stabilize renal cellular structures.

Overall, these findings indicate that Schiff bases, especially compound B, exhibit significant nephroprotective potential against gentamicin-induced renal toxicity, as supported by both biochemical and histopathological evidence. Schiff bases could therefore represent promising lead molecules for the development of novel therapeutic agents aimed at preventing or reducing drug-induced nephrotoxicity. Further mechanistic investigations are needed to elucidate their precise protective pathways and clinical applicability.

Further mechanistic and biochemical studies are recommended to demonstrate the exact pathways involved in their nephroprotective effects and to explore their clinical applicability.

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ISSN: (e) 3007-1607 (p) 3007-1593

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