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THE EFFECT OF SCHIFF BASE [N-N(ETHANE-1,2-DIYL) BIS (1-PHENYL METHANIMINE)] ON PATHOGENIC BACTERIA INDUCED HISTOLOGICAL CHANGES IN RATS LIVER AND KIDNEY

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ABSTRACT : Schiff bases (SB) are aldehyde- or ketone-like compounds in which the carbonyl group is replaced by an imine or azomethine group. The Present study was carried to test the antibacterial activity of newly formed SB against two strains of bacteria (*Staphylococcus aureus* and *Salmonella typhi*) in rats liver and kidney that are infected dermally by comparing its activity with Ofloxacin (OFX) antibiotic. The results of antimicrobial screening, indicate that Schiff bases show significant activity against tested bacteria. Twenty-eight male albino rats used in all *in vivo* experiments. Rats were randomly divided into the following groups (n = 4): G1: untreated rats, G2: *S. aureus* (1.5×10^8 bacteria /ml). G3: *S. aureus* bacteria+ treatment (50mg/ml) consisting of 0.5g of Schiff base added to 9.5g of Vaseline. G4: Ofloxacin (15µg) + *S. aureus*. G5: *S. typhi* (1.5×10^8 bacteria /ml). Group 6: *S. typhi* + treatment (50mg/ml) consisting of 0.5g of Schiff base added to 9.5g of Vaseline . G7: *S. typhi* bacteria + Ofloxacin antibiotic (15µg). These pathogenic bacteria caused many histopathological changes like sever hemorrhage, inflammation, and necrosis in both organs. The antibacterial activity of the Schiff base was investigated (*in vivo*) by treating burned rat skin infected with tested bacteria mentioned previously. Kidney and liver of the treated rats showed that SB revealed great antibacterial activity by recovering the histological architecture of both organs approximately to the normal state unlike OFX, which failed in recovering damaged tissues.

Key words : Schiff base, ofloxacin, *S. typhi*, *S. aureus*, liver, kidney, rat.

INTRODUCTION

Schiff bases (SBs), which are a class of compounds containing an azomethine group (-C=N) (Barrajaa *et al*, 2005). The design of new Schiff bases with antibacterial properties has received considerable attention for many years because it contains anions in biological systems and their crucial role in medicinal, catalytic and environmental chemistry (Meenachi, 2014). Schiff bases and their complexes are ligands of condensation reactions of primary amines and carbonyl compounds with a broad range of biological activities such as antibacterial, antifungal and anticancer characteristics; they can thus be considered promising agents for pharmaceutical and industrial applications (Arulmurugan *et al*, 2010). A number of Schiff base holds anti-inflammatory, allergic inhibitors reduc-ing activities and radical scavenging (Hadjipavlu-Litina and Geronikaki, 1998) and anti-oxidative actions (Xu-Yang *et al*, 2002), antioxidant and hepatotoxic activities which demonstrated by hydroxyurea derivative SBs (Parlak *et al*, 2017). Many other studies have demonstrated that Schiff base amino acid derivatives picolinyl-L-phenylalaninate (PLP), picolinyl- L-tryptophanate (PLT) and nicotinyl-L-tryptophanate (NLT) are capable of scavenging free-radicals, elevating the capacities of antioxidant and the immune system in radiation injury and possessing anticytotoxic, antigenotoxic and antimutagenic properties (Malakyan *et al*, 2016). Staphylococci are diverse ubiquitous opportunistic colonizers of human epithelia involved in nosocomial infections that cause diseases of major importance in both human and animals, ranging from minor skin infections to life-threatening bacteremia as well as septicemia (Aklilu, 1995). Kato *et al* (2010) recorded 18.1% for the prevalence of S. aureus from rats. In the study of Osman *et al* (2016) the liver of the rats infected with *Staphylococcus* group, *Salmonella* spp. Showed many histopathological changes include: a glass and eosinophilic cytoplasm, dilated sinusoids, lymphocytic infiltration in the portal and periportal areas, apoptosis in and necrosis of the hepatocytes.

Findings from the study of Demirci *et al* (2015) have shown the potential effects of the SB complex on

Diethylnitrosamine induced liver carcinoma for the first time. The SB complex not only showed potent apoptotic activity but also anti-inflammatory activity in liver cancer, with no detectable systemic toxicity. It has been reported that the gastric cytoprotection might be mediated by at least two different mechanisms: one of them through prostaglandin synthesis and the second one by increasing the production of mucosal glycoproteins (Favier *et al*, 2005).

Salmonella typhi is a true pathogen, can cause disease in almost any organ of the body. *S. typhi* has been reported to cause the life-threatening infections such as meningitis, endocarditis, myocarditis, empyema, and hepatic abscess. Renal involvement by *S. typhi* is a relatively rare presentation. A case of renal abscess caused by *S. typhi* isolated for the first time in 10-year-old child from the renal abscess, and interestingly this isolate was found to be resistant to quinolones (Kaur, 2015).

Ofloxacin (OFX) belongs to the class of Fluroquinolones antibiotics. This class of antibiotic is used for the treatment of both gram positive and gram negative bacterial (Naveed and Hamid, 2015). The increase in the mortality rate associated with infectious diseases is directly related to bacteria that exhibit multiple resistance to antibiotics. The lack of effective treatments is the main cause of this problem (Alekshun and Levy, 2007). The development of new antibacterial agents with novel and more efficient mechanisms of action is definitely an urgent medical need (Rice, 2006). In the light of such evidence, synthesis of new SB agents with diverse biological activities has generated interest in the field of pharmacological science. The present study was carried to test the antibacterial activity of newly formed SB against two strains of dermally infected bacteria (*Staphylococcus aureus* and *Salmonella typhi*) in the liver and kidney of rats by comparing its activity with (OFX) antibiotic in order to know the best treatment for tolerating bacterial infection.

MATERIALS AND METHODS

Experimental materials

Ethylenediamine, Benzaldehyde, toluene from Sigma-Aldrich. All reagents were commercially available and used without purification.

Synthesis of Schiff base

(N, N' - (ethane-1,2-diyl) bis (1-phenylmethanimine). A solution of ethylenediamine (0.5g, 0.008mol) dissolved in toluene (25mL). It was added with stirring to a mixture of tow mole benzaldehyde (1.76g, 0.016mol) in toluene (25mL) with few drops HBr. The mixture was allowed to reflux under N_2 atmosphere for 45 min using Dean–Stark apparatus and then solvent was removed under reduced pressure to give a yellow solid; yield (1.71g, 87.03%), m.p 115-116°C. (FT IR cm^{-1}): 3002 í(C-H_{aro}), 2985 and 2850 í(C-H_{aliph}), 1639 í(C=N), 1600 í(C=C), 1430 and 1396 $í_{as,s}$ (C-N). NMR data (ppm), δ_H (500 MHz, DMSO-d_6): 3.83 (4H, T, -CH_2-CH_2-), 7.39- 7.72 (10H, Aromatic-H), 8.29 (2H, S, -CH=)(15). The Elemental Analysis for Chemical Formula ((Table1). $C_{16}H_{16}N_2$ has: C, 81.32%; H, 6.82%; N, 11.85(Al-Fahdawi *et al*, 2015).

Biological testing

Preparation of inoculums

Bacterial suspension was prepared according to McFarland standard. A 24 hrs old culture was used for preparation of bacterial suspension. Suspension of organism was made in a sterile normal saline and the turbidity was adjusted such that it contained approximately 1×10^6 CFU/ml. It was obtained by adjusting the optical density of the bacterial suspension to 0.5 McFarland turbidity standards (MacFaddin, 2000).

Diagnosis bacteria

Both bacterial species were isolated from patients with burn infection (*Staphylococcus aureus* and *Salmonella typhi*), they isolated on respective selective and differential media were identified on the basis of colonial, morphological, Gram stain and biochemical tests, Biochemical tests used for identification of bacteria and used API 20E (Khayyal *et al*, 1993).

Antibiotic susceptibility test

The modified Kirby-Bauer method was carried out to determine the susceptibility of obtained isolates to some antibiotics such as Ceftazidime (CAZ) 30µg, Clindamycine (CD) 2µg, Lincomycine (L) 2µg, Chloramphenicol(C) 30µg, Cefixime (CFM) 5µg, Amoxycillin (AMX) 10µg, Cipfloxacin (CPX) 5µg, Cotrimoxazole (COT) 5µg, Augmentin (AUG) 12.5µg, Erythromycin (ERY) 15µg Ofloxacin(OFX), and Nitroforantoin (NIT) 300µg antibiotics as described by (Mackie, 1996).

Bacterial susceptibility testing

Agar diffusion test

Muller Hinton Agar (MHA) (HiMedia, India) was used to determine the diameter of inhibition zone (ID) by the well diffusion methods. The plates were inoculated with the standardized suspension (comparing with McFarland tube) of the test isolates. The plates were to dry in the incubator for 30minutes at 37°C and with the aid of a sterile standard allowed core borer, 5 wells with

Table 1 : Synthesis of Schiff base.

Symbol	í(C-H) Arom.	í(C-H)alipha	í (C=N)	í (C=C)Arom.	í (C-N)
Pre-ligand	3002	29852850	1639	1600	14301396

5mm in diameter were bored at equidistant. Each of the Schiff base dissolved in Dimethyl sulfoxide (10% DMSO), final consternation (50, 100, 150, 200) mg / mL. and 25ìl of each compound was introduced into the appropriate well in the inoculated plate, in addition to sterile water and DMSO was used as negative controls. The prepared plates were incubated at 37°C for 24h. The resulting zones of inhibition were measured using a ruler calibrated in millimeters. The average of the three readings was taken to be zone of inhibition of the bacterial isolates in question at that particular concentration (Junaid *et al*, 2006).

Determination of minimum inhibitory concentration (MIC)

The above-mentioned compound (Schiff base) that showed antimicrobial activity were later tested to determine the MIC for each bacterial isolates. Two bacterial species *S. aureus*, *S. typhi* were grown in nutrient broth tubes separately for 6 h. Afterwards, 100 µL of 10^6 cells/mL of growth culture were inoculated in nutrient broth tubes containing different concentrations of the Schiff base (0,10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150 mg/ml) for 24 h at 37°C for each bacteria in addition to control samples, then the bacterial growth was evaluated on the basis of the turbidity of the suspension and all tubes were read by spectrophotometer at 620nm (C.L.S.I, 2011).

Experimental design

Twenty-eight male albino rats (*Rattus norvegicus*) (150-180 g) bw. aged 10-12 week were used for all in vivo experiments. This experiment performed in May 2018 in department of Biology, College of Education, Salahaddin University, Erbil city. They were kept in a light, food and temperature-controlled room and all rats were acclimatized for at least 1 week prior to beginning the experiments. The dorsal back skins of the rats were shaved, antiseptic by ethanol (70%) then burned by using inflamed knife then contaminated with both bacteria *S. aureus* and *S. typhi* (1.5×10^8 bacteria/ml). After two days of injury the inflammation, redness and suppuration region were observed and the experimental rats were randomly divided into the following groups (n = 4):

Group 1: Control group (untreated rats)

Group 2: Rats infected with *S. aureus*.

Group 3: Rats treated with ointment for *S. aureus* bacteria (concentration 50mg/ml) consisting of 0.5g of Schiff base added to 9.5g of Vaseline.

Group 4: Rats treated with ointment composed of antibiotic for *S. aureus* bacteria (OFX) 15µg.

Group 5: Rats infected with *S. typhi*

Group 6: Rats treated with ointment for *S. typhi* (concentration 50mg/ml) consisting of 0.5g of Schiff base added to 9.5g of Vaseline.

Group 7: Rats treated with ointment composed of antibiotic for *S. typhi* bacteria (OFX) 15µg.

The treatments applied on the burned skin of rats and continued twice each day during 15 consecutive days and the numbers of bacteria was calculated (Umachigi, *et al*, 2008).

Anesthesia, Dissection

All animals were anesthetized with ketamine (35mg/kg B.W.) and xylazine (5mg/kg B.W.) (Laird *et al*, 1996), sacrificed at the end of experiment. Liver and kidney divided into small pieces (less than $0.5cm^3$ thickness) then kept in fixative.

Histopathological Examination (Paraffin Method)

Specimens of liver and kidney fixed by 10% formaldehyde. Then processed for paraffin method by dehydrating through serial dilutions of alcohol (80% for 1/2 hour, 96% two changes each for 2 hours, cleared in xylene for 2 hours, dried and infiltrated in paraffin wax at 60°C, then embedded in paraffin wax. Paraffin blocks were prepared for sectioning at 4 µm thickness section. The obtained tissue sections were collected on glass slides, deparaffinized by xylol and rehydrated by descending serial of ethanol, then stained by gill hematoxylin for 20 minutes, washed by tap water for 2 minutes then stained by eosin for 3 minutes followed by dehydratetion via ascending serial of alcohol. Finally, cleared by xylol, mounted with Canada balsam (Al-Kinani, 2013).

RESULTS AND DISCUSSION

Biological activity

All bacterial isolates were tested for antimicrobial susceptibility testing using disk diffusion methods and the results were interpreted according to standard values provided by Clinical and Laboratory Standard Institute of antimicrobial susceptibility testing (C.L.S.I, 2011). Table 2 illustrate the susceptibility profile for all isolates by using 12 antimicrobial agents. Isolated bacteria showed a variation in their sensitivity and resistance to used antibiotics, on other hand, the high resistance of the bacterial isolates may be related to the presence and

Table 2 : Antibiotic susceptibility of bacterial species under the study.

Microorganism	MIC
	Schiff bases
Staph. aureus	100
Salmonella typhi	80

Means no inhibition.

Table 3 : Inhibition zones (mm) of Schiff base against bacteria.

Chemical Comps. / Bacteria species	Schiff base				
	200 (mg/mL)	100 (mg /mL)	50 (mg/mL)	25 (mg/mL)	OFX (mg/mL)
Staphyococcus aureus	15	12	10	8	32
Salmonella typhi	20	15	12	-	30

disseminations of the plasmids within heterogeneous populations of these bacteria (Anderson, 2005) or may be due to that majority of the populace sampled purchases antibiotics in the open markets without any medical prescription, use of wrong concentration and for wrong diseases. The development of drug resistance in human pathogens against commonly used antibiotics has necessitated a search for new antimicrobial substances (Erdogrul, 2002).

The result of antibacterial activity of Schiff bases for selected bacteria revealed that the inhibition zone (8-20mm), as shown in Table 3. Antibacterial activity of SB shows ascending order, when we increase concentration, area of inhibited growth also increased. The results of antimicrobial screening, indicate that Schiff bases show significant activity against *Staphylococcus aureus,* and *Salmonella typhi*. The MIC of SBs were ranged between (100- 80 mg/ml.) (Table 4). Our result is supported by the study of Manikpuri *et al* (2010), who prepared SB of Salicaldehyde and sulfonamides. The SBs were tested for the biological significance. The antimicrobial screening SBs showed significant results against some species of *Salmonella* and *Staphylococcus* bacteria. While studying the effects of concentration on zone of inhibition of each compound, the novel SBs gave excellent response against *S. aureus* at all chosen concentration.

The *in vivo* assay revealed that the treatment of infected rats skin with MIC for SB and (OFX) antibiotic during 15 days, it was found to have marked effects (Significant at P≤0.001) on the number of *Staphylococcus aureus* and *Salmonella typhi* and the number of bacteria was reduced (when compaird with antibiotic) significantly (P≤0.001) from 180×10^6 cell/ml and 170×10^6 cell/ml during the treatment days. The results showed that the skin of the infected rat could be cured by the tumor's disappearance, redness and disappearance of the pus from the affected area after treatment for 15 days using the antibiotic ofloxacin and SB compared to control, where the area of the infection remained wet and continuously scrubbed (Table 5). Our result is agreed with the study of Alwan *et al* (2014), who made an interesting approach of synthesizing a new series of pyridopyrimidine derivatives containing Schiff bases of certain amino acids The Schiff bases showed good to moderate antibacterial activity against some gram-positive bacteria. However, the Schiff bases of the aromatic amino acids, showed better antimicrobial activities compared with those of aliphatic amino acids.

Histological study

Effect of SB and OFX on rat liver infected with pathogenic bacteria

Salmonella infection occurs worldwide and is still an important public health problem in many developing countries. The infection can affect almost all major organs including the liver (Albayrak *et al*, 2011). Liver sections

Table 4 : Minimum inhibitory concentration (MIC) of SB on bacterial species.

Bacterial species	CAZ	C	CFM	CD	L	AMX	STR	COT	AUG	ERY	NIT	OFX
Staphylococcus aureus	R	R	S	S	R	S	S	R	R	R	R	S
Salmonella typhi	S	S	R	R	S	S	R	S	R	R	R	S

Table 5 : Numbers of *Staphylococcus aureus* and *Salmonella typhi* between the rat's groups.

Duration of treatment per day	Group(1) Control	Group(2) OFX *S. aureus*	Group(3) OFX *S.typhi*	Group (4) *Staph aureus* Schiff bases 50mg/ml	Group(5) *S.typhi* Schiff bases 50mg/ml
3	0	140	160	180	170
6	0	120	110	70*	110
9	0	65	40	30*	50
12	0	30	0	20	35*
15	0	0	0	5	10

*Significant at P≤0.001

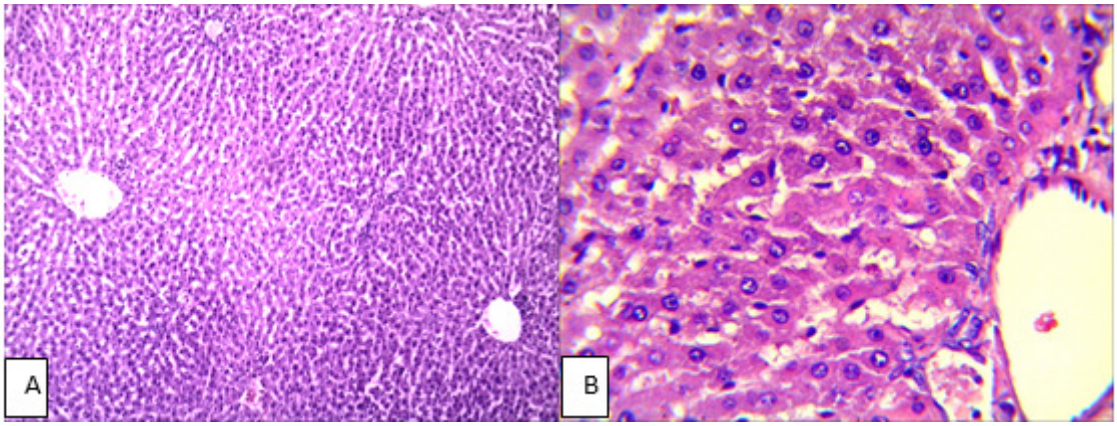

Fig. 1 : A-B Photomicrograph from control rat liver shows normal histological structure of hepatic lobules and central vein100x and 400x respectively H&E).

obtained from the control group rats showed a normal histological architecture for the hepatic lobule, normal central vein and hepatic plate were shown (Fig. 1. A, B). However, rats infected with *S. typhi* showed many histopathological changes including dilation of the hepatic vein, highly inflammatory infiltration around both central and portal vein as well as hemorrhage distributed between the hepatic plates (Fig. 2 A, B). The same histopathological changes in liver of rats infected with *S. aureus* were observed included dilation of the hepatic vein, hemorrhage and inflammatory cell infiltration (Fig. 3 A,B), these finding were correspond with that of Osman *et al* (2016), which revealed that histopathological examination of the liver of infected rats with *S. typhi*, and *S. aureus* revealed swollen hepatocytes with decreased sinusoidal spaces and widely distributed necrotic foci.

While treating with SB recovered the liver nearly to the normal state and cellularity, reduced bacterial induced inflammation and hemorrhage (Fig. 2 C, D). Demirci *et al* (2015) revealed that administration of SB decreased the incidence and the number of hepatic nodules in a dose dependent manner by regulating inflammation response and the apoptotic pathway and this result also were agree with those of the current study. Histopathological finding of Schiff base ligand derived from the condensation reaction of tryptamine (an indole derivative) and 5-nitrosalicylaldehyde (TNS) showed marked gastric protection against ethanol-induced gastric ulcer in rats along with reduction of edema and leucocytes infiltration of the submucosal layer (Ibrahim *et al*, 2016), which improve the ability of SB in control the inflammatory action induced by toxic material.

Additionally, the study of Salga (2012) showed that the zinc complexes derived from the Schiff bases2-(2-(piperazin-1-yl)ethylimino)methyl)phenol,4-chloro-2-(2-(piperazin-1-yl)ethylimino) methyl) phenol and 4-bromo-2-(2-(piperazin-1-yl)ethylimino)methyl) phenol have fewer toxic effects based on the insignificant changes observed in the behavioral, hematological, immunological and biochemical parameters in rats. However, a decrease in the activity of liver enzymes AST, ALT, ALP was noted.

Our study revealed that Salmonella infected rats treated with OFX showed little recovering of the liver tissue (Fig. 2 E, F). Ofloxacin drug alone cause adverse effects on rat hepatic and renal parameters, due to enhancement of oxidative stress product production like MDA while combining it with metronidazole protect these organs from free radical damages (Ahmad, 2010). This is agreed with our study since liver tissue recovery by this drug is rare (Fig. 3 E.,F). Obaleye (2010) revealed in his study that OFX and metal complexes causes adverse effects on the liver by decreasing its weight.

Effects of Schiff base and Ofloxacin on rat kidney infected by pathogenic bacteria

Kidney sections from control group rats showed normal histological feature of glomerulus, proximal and distal convoluted tubules (Fig. 4 A, B), while kidney of rats infected with S. typhi bacteria showed marked histopathological changes in the cortex and outer medulla, including highly hemorrhage in the glomerulus and between the tubules (Fig. 5 A, B), this is agreed with the study of Hahna and Sohnlea (2013), they concluded from their experiment that after skin surface application the bacteria rapidly distributed to lymph nodes, spleen, kidneys and other organs. *S. aureus* can also spread from skin to deep organs by a non-bacteremic process. The immunosuppressed mice inoculated epicutaneously also had bacteria invading from the liver surface. It supports our results that bacteria infected through the skin can reach internal organs.

The skin possess a rich lymphatic system that drains

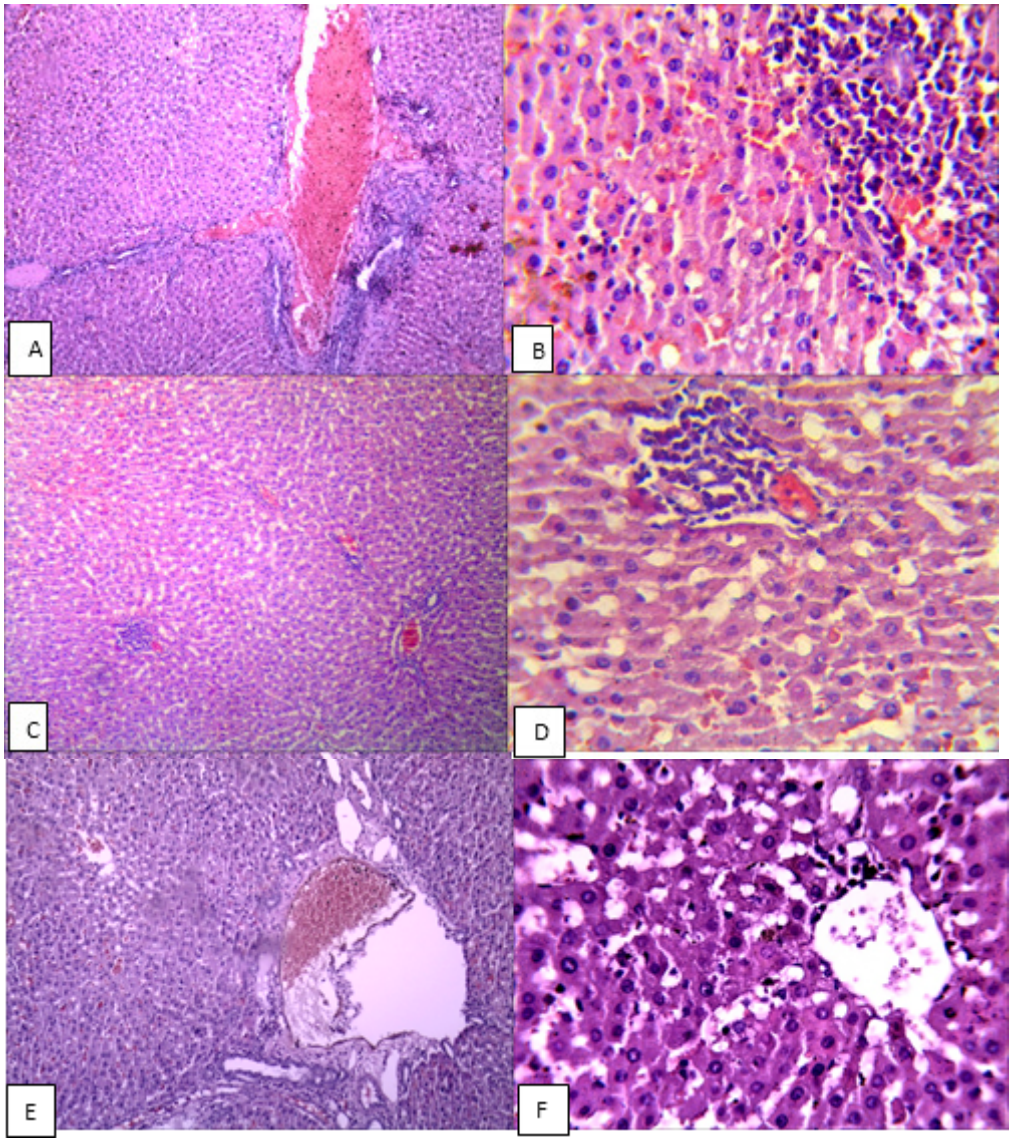

Fig. 2 : A, B - Photomicrograph from *S. typhi* infected rat liver (100x and 400x respectively), C, D- photomicrograph from *S. typhi* infected rat liver treated with SB (100x and 400x respectively) and E, F- photomicrograph from *S. typhi* infected rat liver and treated with OFX (100x and 400x respectively) (H&E).

away lymph originating from epidermal interstitial fluid; it consists of a complex vasculature that eventually combined with larger lymphatics such as the thoracic duct (Oliver and Detmar, 2002). The latter terminates in the venous system, indicating that bacteria in major lymph vessels may end up in the bloodstream. Drainage of staphylococci to the renal lymph nodes is another possibility (Harrell *et al*, 2008).

Epicutaneous inoculation may cause entry into interstitial fluid over a large surface area, thereby augmenting travel to deep organs. Such travel means crossing intervening tissue planes, as with bacteria translocating from the gut. The kidney occupies a retroperitoneal location and the outer connective tissue site may be more directly connected to the inoculated skin than is the rest of the organ. Carriage by host immune surveillance cells (*i.e.*, macrophages or epidermal Langerhans cells) might be possible, but the rapid times involved and unusual distribution in the kidney make this consideration less likely. Staphylococci themselves are non-motile, but locomotive force could be applied to interstitial fluids containing them by respiration or other animal movements (Ikomi, 1996).

Treating rats with SB greatly reduced hemorrhage induced as compared to *S. typhi* infected group and nearly restored normal histological structures of kidney (Fig. 5 C, D), all these investigations were demonstrated by other studies, which showed that no increase in serum biochemical parameters was detected in SB-treated animals induced by cisplatin which caused different degeneration feature in the kidney of treated rats include, extensive epithelial swelling in the renal tubules with

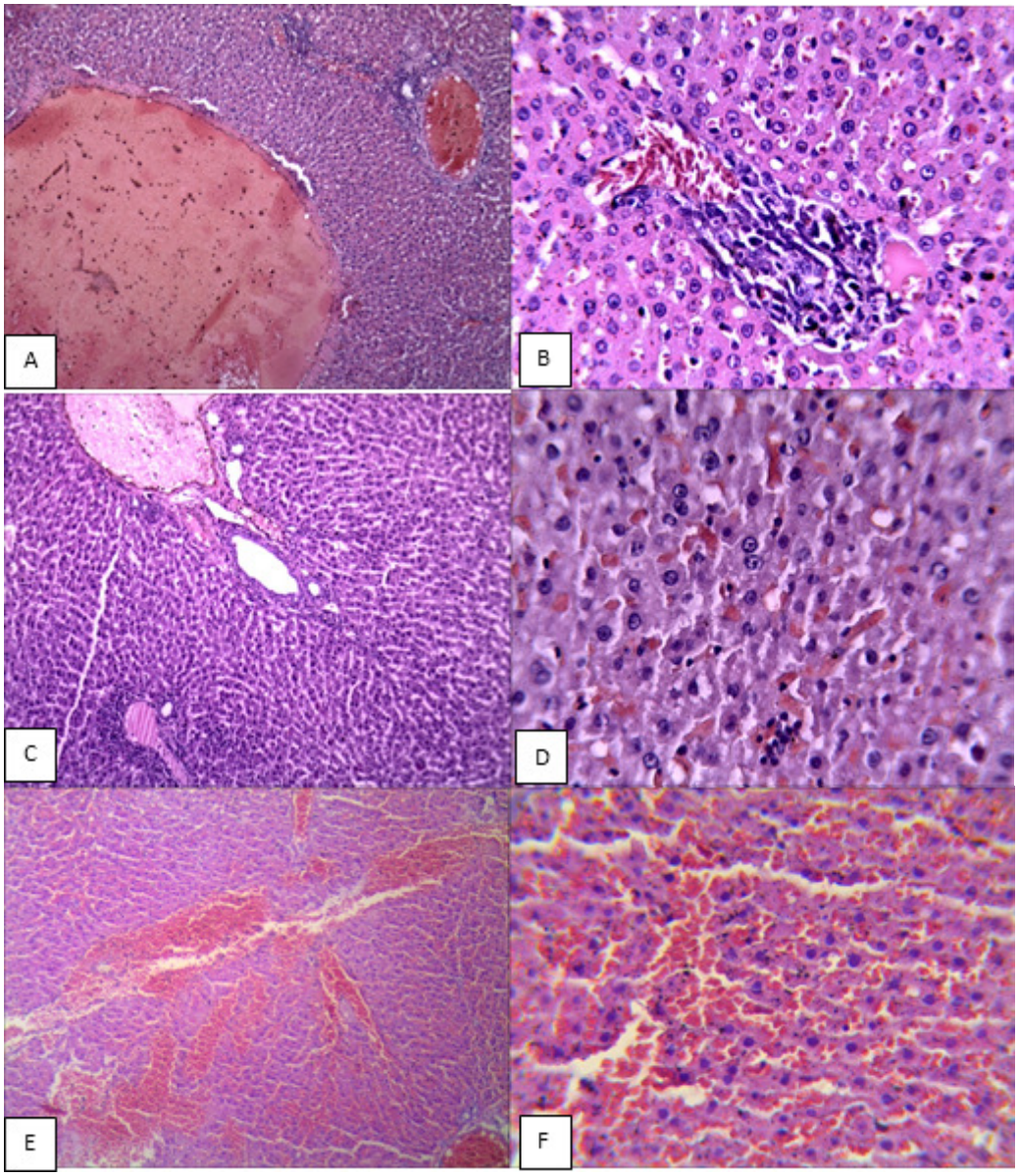

Fig. 3 : A, B- Photomicrograph from *S. aureus* infected rat liver (100x and 400x respectively), C, D- photomicrograph from *S. aureus* infected rat liver treated with SB (100x and 400x respectively) and E,F- photomicrograph from *S. aureus* infected rat liver and treated with OFX (100x and 400x respectively) (H&E).

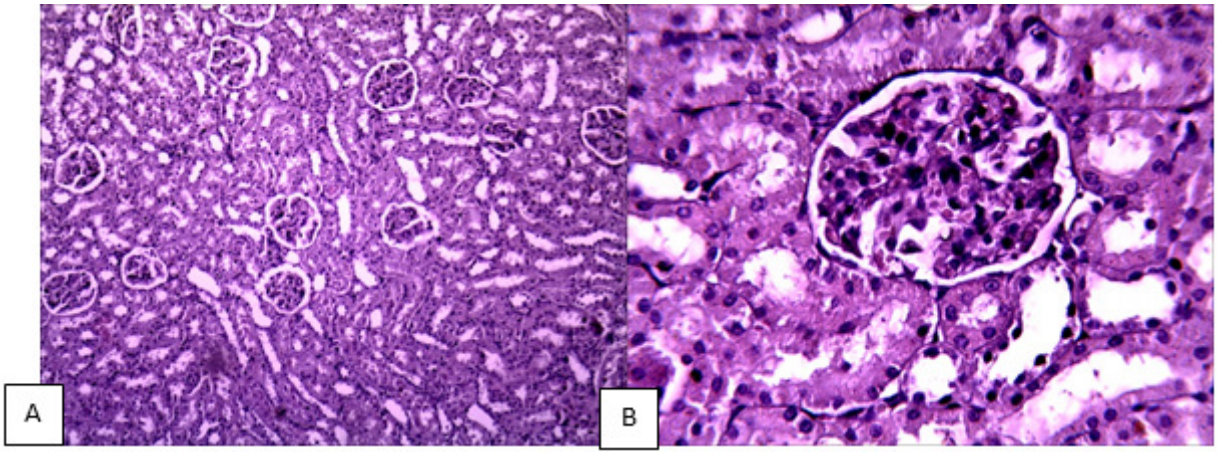

Fig. 4 : A, B- photomicrograph through the kidney Control group rats shows the normal histological structure of kidney glomeruli, proximal and distal convoluted tubules (100x and 400x respectively) (H &E).

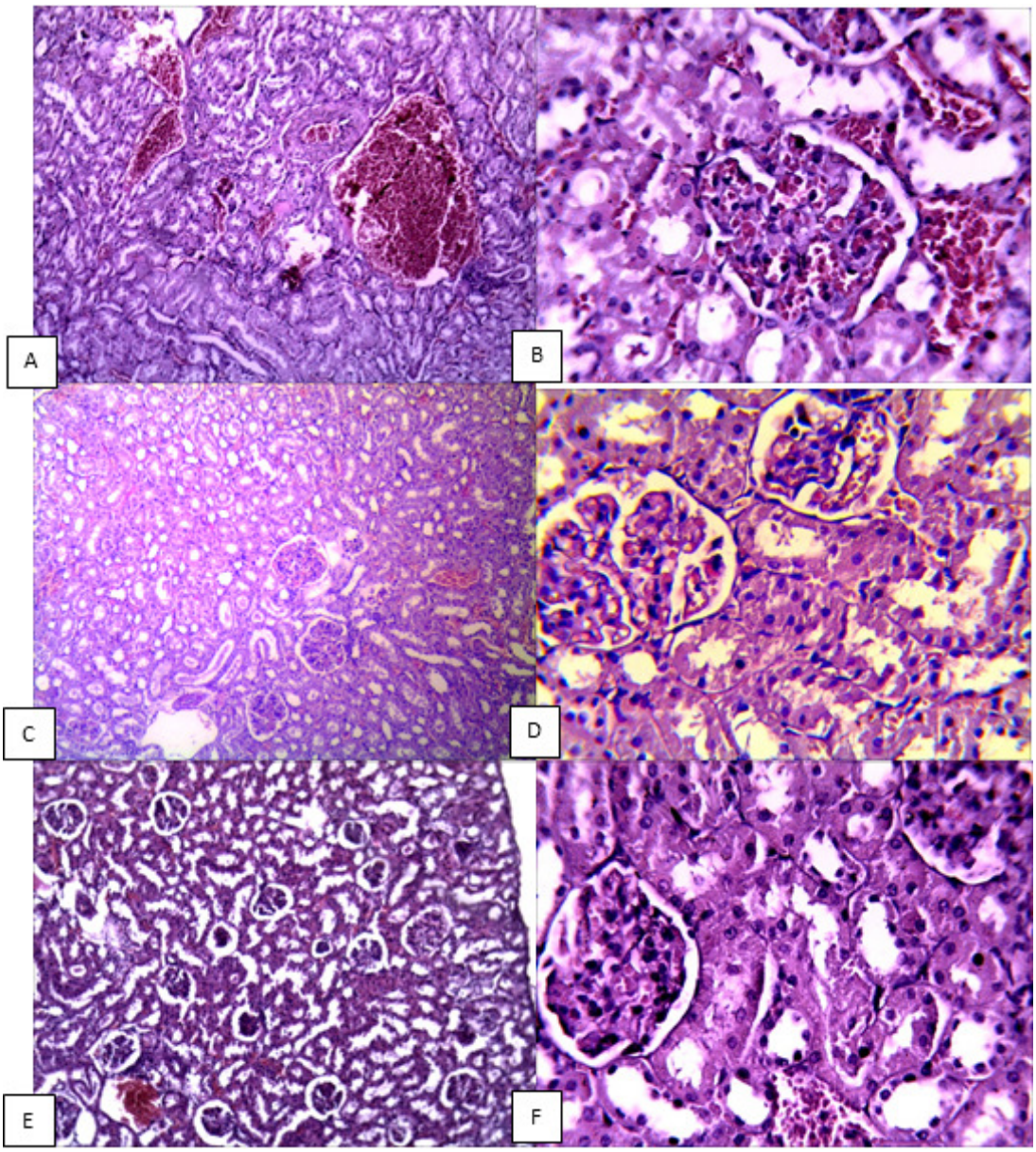

Fig. 5 : Photomicrograph through the kidney of A, B- *S. typhi* group (100x and 400x respectively), C,D- *S. typhi* and SB(100x and 400x respectively), E, F- SAL and OFX (100x and 400x respectively) (H&E).

decreased lumen space and generalized necrotic changes with interstitial hemorrhage in renal cortex were found, also cisplatin increased serum urea nitrogen and creatinine levels (Osman *et al*, 2016).

While the study of the kidney sections from the cisplatin-treated rats showed marked histological changes in the cortex and outer medulla, including vacuolation, interstitial edema, tubular atrophy, severe tubular necrosis, and interstitial inflammation. When administered together with cisplatin, SB reduced cisplatin-induced tubular necrosis (Demirci *et al*, 2015).

On the other hand treatment with OFX for Salmonella group showed slightly hemorrhage and degeneration of some glomerulus (Fig. 5 E, F).

More pathological changes were observed in the kidney of *S. aureus* infected group revealed highly infiltration of lymphocyte inflammatory cells beside wide range of hemorrhage between the tubules when compared with control group rats (Fig. 6 A, B), while in the section of the S. aureus infected group treated with SB substance a well-recognized recovering for the kidney tissue were seen, whereas no inflammatory cells appeared also hemorrhage between the tubules were decreased (Fig. 6 C, D).

Finally, results showed that OFX ointment failed in the treating of the abnormalities induced by *S. aureus* bacteria for the kidney tissue in order the highly blood distribution between the kidney tubules and inside the

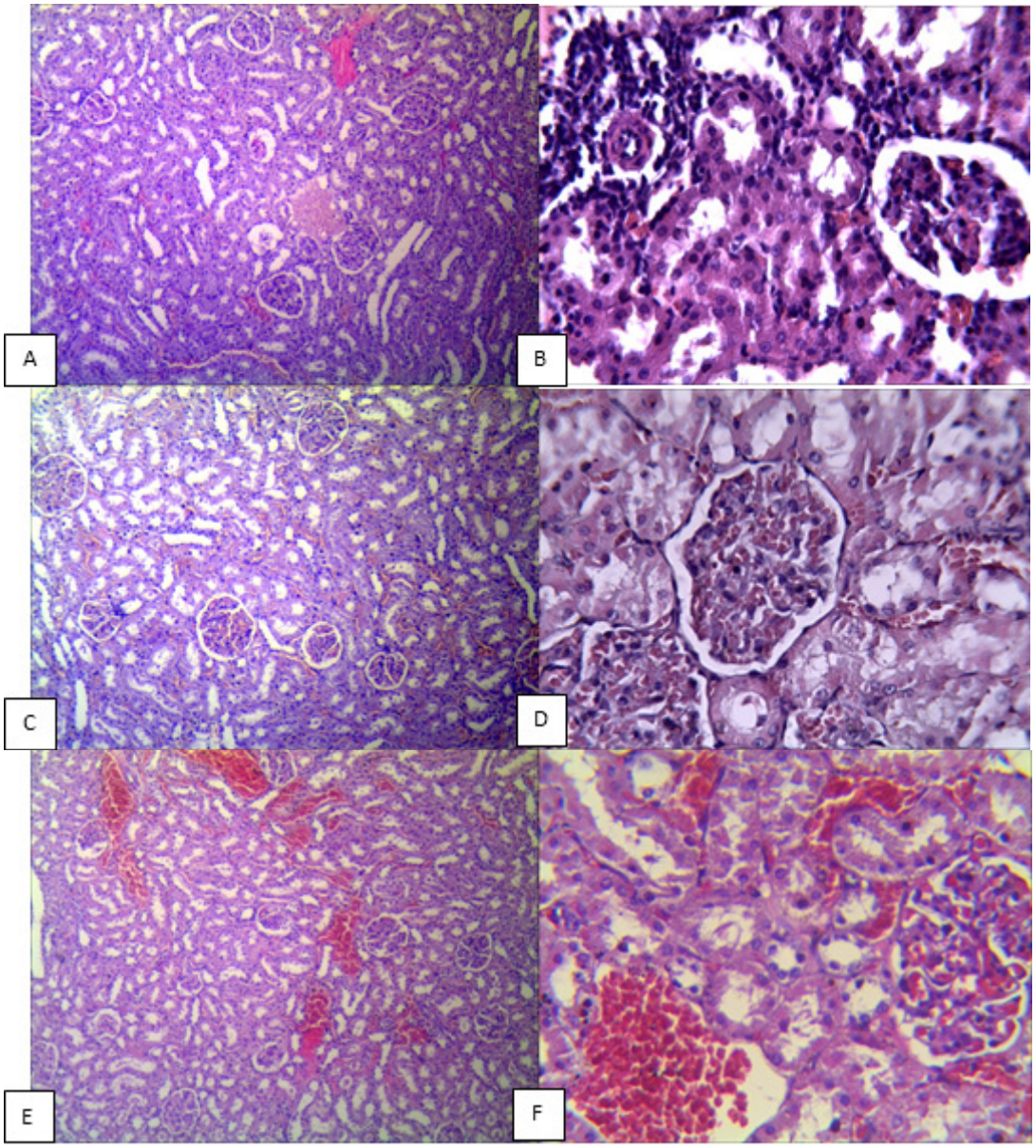

Fig. 6 : Photomicrograph through the kidney of A, B- *S. aureus* group (100x and 400x respectively), C,D- *S. aureus* and Schiff base (100x and 400x respectively), E,F- *S. aureus* and OFX (100x and 400x respectively) (H&E).

glomerulus were still observed (Fig. 6 E, F). This is agreed with the study of Lomaestro (2000), Montaganc *et al* (2005), who revealed that antimicrobials cause nephrotoxicity like tubular necrosis and vascular necrosis.

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