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Protective and Curative Effects of Sider Honey and Vitamins A, C, and E against Penicillin- and Streptomycin-Induced Nephrotoxicity in Guinea Pigs

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Abstract

Bacterial infections pose a significant health risk, particularly in developing countries where antibiotics like penicillin and streptomycin are commonly used. However, these antibiotics can lead to nephrotoxicity by generating reactive oxygen species (ROS), which cause oxidative stress and damage to the kidneys. This study aimed to evaluate the protective and therapeutic effects of Ziziphus spina-christi (Sidr) honey, along with vitamins A, C, and E, both individually and in combination, against kidney damage induced by penicillin and streptomycin in guinea pigs. A total of 200 guinea pigs were divided into 20 groups, each containing 10 animals. Groups 1–13 received concurrent treatments with antibiotics and antioxidants over a period of 30 days, while groups 14–20 were treated with antioxidants following 20 days of antibiotic administration. We assessed renal function markers, including urea, uric acid, and creatinine levels, and conducted histological analyses of kidney tissues. The results indicated that both Sidr honey and the vitamins significantly reduced levels of urea, uric acid, and creatinine compared to the groups treated solely with antibiotics, demonstrating improved renal function. Histological analysis also showed decreased kidney damage, with the combination of vitamin treatments offering the most substantial protection. The study concluded that Sidr honey and vitamins A, C, and E effectively reduce antibiotic-induced nephrotoxicity, emphasizing their potential as therapeutic agents for preserving kidney health. Further research is recommended to explore their clinical applications.

Keywords: Nephrotoxicity, Sidr honey, Vitamins A, C, E, Penicillin toxicity, Streptomycin toxicity

الملخص: تعد العدوى البكتيرية مصدر قلق صحي كبير، خاصة في البلدان النامية حيث يُستخدم المضادات الحيوية مثل البنسلين والستربتوميسين بشكل واسع. ومع ذلك، يمكن أن تسبب هذه المضادات الحيوية سمية كلوية من خلال إنتاج أنواع الأكسجين التفاعلية (ROS)، مما يؤدي إلى الإجهاد التأكسدي وتلف الكلى. قيّمت هذه الدراسة التأثيرات الوقائية والعلاجية لعسل السدر وفيتامينات أ وج وه، منفردة ومجتمعة، ضد التلف الكلوي الناتج عن البنسلين والستربتوميسين في خنازير غينيا. تم تقسيم 200 خنزير غينيا إلى 20 مجموعة، كل مجموعة تضم 10 حيوانات. تلقت المجموعات من 1 إلى 13 علاجًا متزامنًا مع المضادات الحيوية ومضادات الأكسدة لمدة 30 يومًا، في حين تلقت المجموعات من 14 إلى 20 علاجًا لاحقًا بمضادات الأكسدة بعد 20 يومًا من إعطاء المضادات الحيوية. تم قياس مؤشرات وظائف الكلى (اليوريا، وحمض اليوريك، والكرياتينين) وتحليل أنسجة الكلى نسيجيًا. أظهرت النتائج أن عسل السدر والفيتامينات قللت بشكل ملحوظ مستويات اليوريا وحمض اليوريك والكرياتينين مقارنة بالمجموعات التي تلقت المضادات الحيوية فقط، مما يشير إلى تحسن وظائف الكلى. وكشفت التحليلات النسيجية عن انخفاض تلف الكلى، حيث أظهر العلاج المركب بالفيتامينات أفضل حماية. خلصت الدراسة إلى أن عسل السدر وفيتامينات أ وج وه فعالة في تقليل السمية الكلوية الناتجة عن المضادات الحيوية، مما يشير إلى إمكانياتها كعوامل علاجية للحفاظ على صحة الكلى. توصي الدراسة بمزيد من البحوث لتطبيقها في الممارسات السريرية.

1. Introduction

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Bacterial infections pose a major public health challenge, particularly in developing countries, such as Yemen, where antibacterial therapy remains essential [1]. Antibiotics such as penicillin and streptomycin are widely prescribed to combat these infections [2]. However, along with their therapeutic benefits, antibiotics are among the leading causes of drug-induced side effects, including renal toxicity [3]

Penicillin and streptomycin are known to induce nephrotoxicity, primarily by generating excessive reactive oxygen species (ROS). Oxidative stress disrupts cellular antioxidant defenses and enhances lipid peroxidation, leading to kidney cell damage [4,5]. Given the crucial role of kidneys in filtering toxins, this damage can significantly impair renal function [6].

Antioxidants offer a promising solution by neutralizing free radicals and protecting cellular structures from oxidative damage [7]. Naturally occurring antioxidants, especially vitamins A, C, and E, are powerful free-radical scavengers that protect proteins, DNA, and cell membranes from oxidative injury [8, 9]. Honey, rich in polyphenols such as flavonoids and tannins, has shown potent antioxidant and free radical-scavenging activities [10, 11,12].

Although the protective and curative effects of antioxidants have been studied, there is limited research on the specific effects of Sidr honey and combined vitamins A, C, and E on kidney damage induced by penicillin and streptomycin. This study aimed to evaluate the nephroprotective and nephrocurative potential of Sidr honey and vitamins A, C, and E (individually and in combination) in mitigating the adverse renal effects caused by penicillin and streptomycin. This study aimed to provide insights into antioxidant-based strategies for protecting and restoring kidney function in antibiotic-induced nephrotoxicity.

2. Materials and Methods

2.1 Animals

Adult male guinea pigs (5-6 months old, 800-900 g) were obtained from Sana'a Zoo, Yemen, Brazil. The animals were housed in the animal facility of the Biology Department at Sana'a University under standard conditions at room temperature and acclimatized for an additional 30 days. They were provided with a standard laboratory diet and water ad libitum, following the *Guide for the Care and Use of Laboratory Animals*[13].

2.2 Chemicals (Antibiotics and Vitamins)

Penicillin and Streptomycin were obtained from Ave Group (USA-Colombia-Mexico). Vitamin C was sourced from Carlo Erbo, Italy; Vitamin E from Merck, Germany; and Vitamin A from Look for Chemical, China. Natural Ziziphus spina-Christi honey was purchased from a beekeeper in Mabian, Hajja, and Yemen.

2.3 Diagnostic Kits and Reagents

Diagnostic kits for urea, uric acid, and creatinine were sourced from Spinreact, S.A., and Ctra. Santa Coloma, 7 E-17176 Sant Esteve de Bas, Spain. All other chemicals and reagents were of the highest commercially available purity.

2.4 Experimental Design and Schedule

The experiment consisted of two parts:

Part 1: This section evaluated the efficacy of antioxidants (Sidr honey and vitamins A, C, and E, administered separately and in combination) as co-treatments to counteract the adverse effects of penicillin and streptomycin. A total of 130 guinea pigs were randomly divided into 13 groups (10 animals per group) and treated as follows:

- **Group 1:** Control group; intraperitoneally injected with normal saline and orally administered 0.5 ml corn oil daily for 30 days.
- **Group 2:** Penicillin-only group, injected with 50000 IU/kg body weight (b.w.) penicillin daily for 30 days.
- **Groups 3–7 (Penicillin + Antioxidants):** Treated with 50000 IU/kg b.w. Penicillin, co-administered with either 600 mg/kg b.w. Sidr honey (G3), 10000 IU/kg b.w. vitamin A (G4), 100

mg/kg b.w. vitamin C (G5), 100 mg/kg b.w. Vitamin E (G6), or a combination of vitamins A, C, and E (G7) for 30 days.

- **Group 8:** Streptomycin-only group, injected with 50 mg/kg b.w. Streptomycin daily for 30 days.
- **Groups 9–13 (Streptomycin + Antioxidants):** treated with 50 mg/kg b.w. Streptomycin, co-administered with either 600 mg/kg b.w. Sidr honey (G9), 10000 IU/kg b.w. vitamin A (G10), 100 mg/kg b.w. vitamin C (G11), 100 mg/kg b.w. Vitamin E (G12), or a combination of vitamins A, C, and E (G13) for 30 days.

Part 2: This part evaluated antioxidants as post-treatments after penicillin or streptomycin withdrawal. Seventy guinea pigs were randomly divided into seven groups (10 animals per group) and treated as follows.

- **Group 14:** The control group, was injected with normal saline for 20 days, followed by 0.5 ml corn oil daily for an additional 20 days.
- **Group 15:** Penicillin-only group; injected with 50000 IU/kg b.w. Penicillin for 20 days, followed by 0.5 ml corn oil daily for an additional 20 days.
- **Groups 16–17 (Penicillin + Post-Treatment):** Treated with 50000 IU/kg b.w. Penicillin for 20 days, then administered either 600 mg/kg b.w. Sidr honey (G16) or a combination of vitamins A, C, and E (G17) daily for the next 20 days.
- **Group 18:** Streptomycin-only group; injected with 50 mg/kg b.w. Streptomycin for 20 days, followed by 0.5 ml corn oil daily for an additional 20 days.
- **Groups 19–20 (Streptomycin + Post-Treatment):** treated with 50 mg/kg b.w. Streptomycin for 20 days, then administered either 600 mg/kg b.w. Sidr honey (G19) or a combination of vitamins A, C, and E (G20) daily for the next 20 days.

2.5 Collection of Blood and Tissue Samples

Twenty-four hours after the final treatment, animals from each group underwent autopsy. Blood samples were taken directly from the heart into sterile tubes, then centrifuged at 3500 rpm for 20 minutes to separate the serum for biochemical analysis. Kidneys were extracted from each guinea pig, with small sections of kidney tissue fixed in 10% neutral formalin for 24 hours, followed by storage in alcohol for histological preparation.

2.6 Estimation of Renal Function

2.7 Serum levels of urea, uric acid, and creatinine were assessed using commercial Spinreact kits and analyzed through spectrophotometry.

2.8 Histological Studies of Kidney

Kidney tissue samples were dehydrated in graded alcohol solutions (80%, 90%, and 100%), cleared in xylene, and embedded in paraffin wax at 58°C. The paraffin blocks were sectioned at 4-5 µm thickness using a rotary microtome (Leica, Germany) and stained with hematoxylin and eosin[14] for histopathological evaluation under a light microscope.

2.9 Statistical Analysis

Data were analyzed with SPSS version 16.0, using one-way Analysis of Variance (ANOVA) followed by Fisher's Protected Least Significant Difference (PLSD) test for post-hoc group comparisons. Results are presented as mean ± SD, with significance considered at $p < 0.05$.

3. Results:

The data in Table 1 indicate that some groups showed non-significant increases in kidney function markers, whereas others demonstrated slight reductions compared to the control group. Specifically, the groups treated with S. honey (G3), vitamin A (G4), vitamin C (G5), and vitamin E (G6), along with penicillin, showed non-significant increases in urea, uric acid, and creatinine levels. In contrast, the group treated with a combination of vitamins A, C, and E (G7) displayed slight non-significant reductions in these parameters.

Table 1**. The effect of antioxidants as co-treatment to reduce the adverse effects induced by penicillin on kidney function tests in guinea pigs.**

Parameter	G1: Control	G2: Penicillin	G3: S.honey + P	G4: Vit A+ P	G5: Vit C+ P	G6: Vit E+ P	G7: Vit A,C&E+ P
Urea mg/dl	38.76±2.14	47.94±2.06†††	39.73±3.79$^{\#\#\#}$	41.15±3.38$^{\#\#\#}$	39.20±2.76$^{\#\#\#}$	39.36±1.97$^{\#\#\#}$	38.86±2.68$^{\#\#\#}$
Uric acid mg/dl	5.05±0.43	6.92±0.24†††	5.38±0.27$^{\#\#\#}$	5.50±0.30$^{\#\#\#}$	5.44±0.22$^{\#\#\#}$	5.35±0.24$^{\#\#\#}$	5.19±0.28$^{\#\#}$
Creatinine mg/dl	0.99±0.10	1.92±0.30†††	1.14±0.11$^{\#\#\#}$	1.18±0.16$^{\#\#\#\dagger}$	1.16±0.19$^{\#\#\#}$	1.14±0.17$^{\#\#\#}$	1.02±0.08$^{\#\#}$

Values are presented as means ± SD, along with the percentage difference from the control group. Comparisons are conducted for each group against the following: (†) control group; (*) group treated only with streptomycin.

The data in Table 2 indicate that administration of streptomycin alone (G8) significantly increased urea, uric acid, and creatinine levels in guinea pigs compared to those in the control group, demonstrating considerable renal stress. However, the group treated with Sidr honey along with streptomycin (G9) showed a non-significant increase in these markers. Additionally, the group co-treated with vitamin A and streptomycin (G10) displayed significant but moderate increases in urea, uric acid, and creatinine levels.

Table 2**. The effect of antioxidants as co-treatment to reduce the adverse effects induced by streptomycin on kidney function tests in guinea pigs.**

Parameter	G1: Control	G8: streptomycin	G9: S.honey + S	G10: Vit A+ S	G11: Vit C+ S	G12: Vit E+ S	G13: Vit A,C&E+ S
Urea mg/dl	38.76±2.14	54.99±5.10†††	40.14±1.79***	41.85±2.26***†	41.69±2.79***	40.51±1.92***	38.84±3.22***
Uric acid mg/dl	5.05±0.43	7.54±0.30†††	5.50±0.24***	5.71±0.21***†	5.63±0.31***†	5.51±0.23***†	5.52±0.25***
Creatinine mg/dl	0.99±0.10	2.17±0.18†††	1.16±0.14***	1.24±0.12***†	1.23±0.13***†	1.17±0.15***†	1.13±0.15***

Values are presented as means ± SD, along with the percentage difference from the control group. Comparisons are conducted for each group against the following: (†) control group; (*) group treated only with streptomycin.

The data in Table 3 demonstrates that penicillin administration alone (G15) led to a significant increase in urea, uric acid, and creatinine levels in guinea pigs, indicating kidney stress. In contrast, the group treated with Sidr honey after penicillin withdrawal (G16) showed an insignificant increase in these parameters, suggesting a protective role of Sidr honey. Additionally, the group treated with a combination of vitamins A, C, and E following penicillin withdrawal (G17) exhibited a slight, non-significant increase in urea, uric acid, and creatinine levels.

Administration of streptomycin alone (G18) significantly increased urea, uric acid, and creatinine levels, showing a marked impact on kidney function. However, the group that received Sidr honey after streptomycin withdrawal (G19) experienced only an insignificant increase in these markers, indicating potential kidney protection. Furthermore, the group treated with vitamins A, C, and E after streptomycin withdrawal (G20) showed a slight, non-significant increase in urea, uric acid, and creatinine levels.

Table 3. The effect of Sidr honey and vitamins A, C, and E in combination in post-treatment to reduce the adverse effects induced by penicillin and streptomycin on kidney function tests in guinea pigs

Parameter	G14: Control	G15: Penicillin	G16: Penicillin then N.honey	G17: Penicillin then vit A, C, E	G18: Streptomycin	G19: Streptomycin then N.honey	G20: Streptomycin then vit A, C, E
Urea Mg/dl	38.65± 2.93	45.17± 3.28††	39.66± 2.3$^{\#\#}$	39.95± 2.03$^{\#\#}$	47.45± 3.37†††	41.23± 3.0$^{\#\#\dagger}$	41.31±3. 44$^{\#\dagger\dagger}$
Uric acid mg/dl	5.06±0 .39	6.14±0 .25†††	5.51±0 .22$^{\#\#\#\dagger}$	5.54±0 .22$^{\#\#\#\dagger}$	6.88±0 .27†††	5.79±0 .24$^{\#\#\#\dagger}$	5.77±0.1 5$^{\#\#\#\dagger\dagger\dagger}$
Creatinine mg/dl	1.01±0 .15	1.57±0 .29†††	1.19±0 .15$^{\#\#\#\dagger}$	1.19±0 .10$^{\#\#\#\dagger}$	1.97±0 .17†††	1.24±1 .12$^{\#\#\#\dagger}$	1.27±0.1 3$^{\#\#\#\dagger\dagger\dagger}$

Values are presented as means ± SD, along with the percentage difference from the control group. Comparisons are conducted for each group against the following: (†) control group; (*) group treated only with streptomycin.

Figure 1: The light micrographs of kidney cortex cross-sections in guinea pigs show that the control group exhibits normal kidney structures. In contrast, penicillin treatment for 30 days led to structural abnormalities, including glomerular shrinkage and thickened blood vessels. Groups treated with Sidr honey or vitamins (A, C, and E) alongside penicillin showed a marked improvement, with the cortex nearly returning to normal.

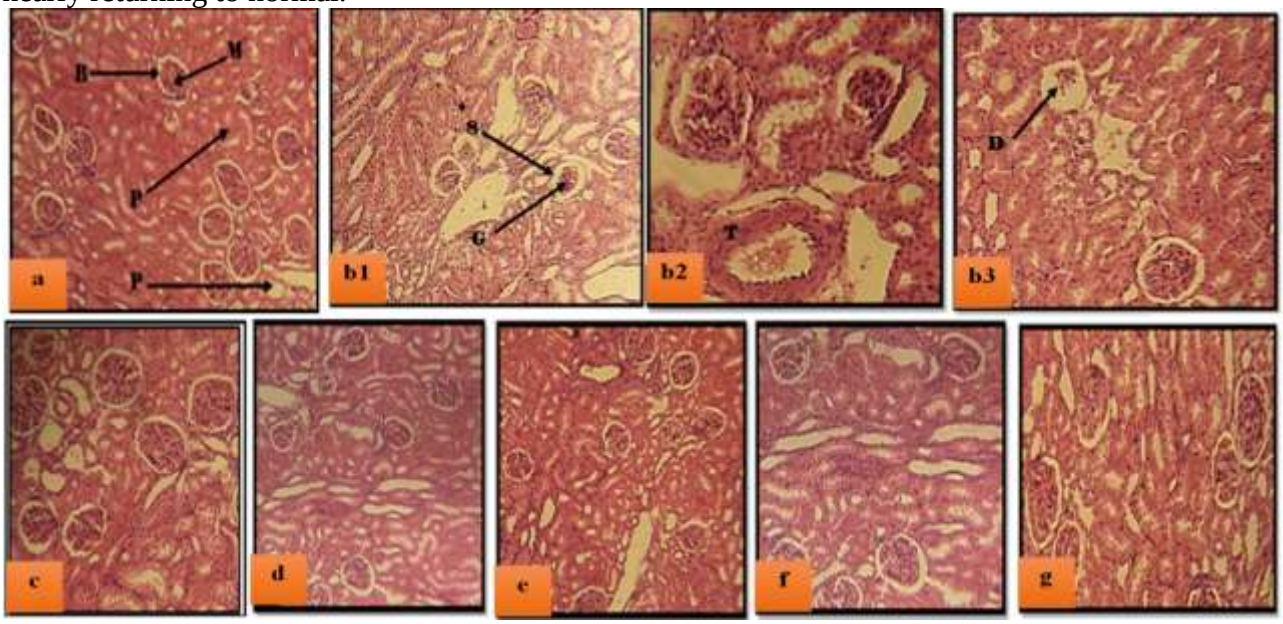

Fig. 1: (a) *Light micrographs of a cross-section in the kidney cortex of control guinea pigs showing normal histological structures of Malpighian corpuscles with its glomerulus (M) Bowman's capsule (B) proximal tubules (P) and distal tubule (D);* ***(b1,2,3):*** *penicillin for 30 days showing dilatation of Bawmn's capsule (S), shrinkage glomerulus (G), glomerular degeneration (D), and thickened blood vessels (T);* ***(c):*** *Penicillin + S.honey;* ***(d):*** *Penicillin + vit A;* ***(e):*** *Penicillin + vit C;* ***(f):*** *Penicillin + vit E;* ***(g):*** *Penicillin + vit A, C&E showing most of the cortex return to normal structure. (H&E X 400).*

Figure 2: In the kidney medulla, control guinea pigs displayed normal collecting tubules, while penicillin treatment for 30 days caused hyperplasia, compressed blood vessels, and hemorrhage. Co-

treatments with Sidr honey or individual vitamins (A, C, and E) showed substantial recovery, and the medulla in the combined vitamins (A, C, E) group returned almost to normal.

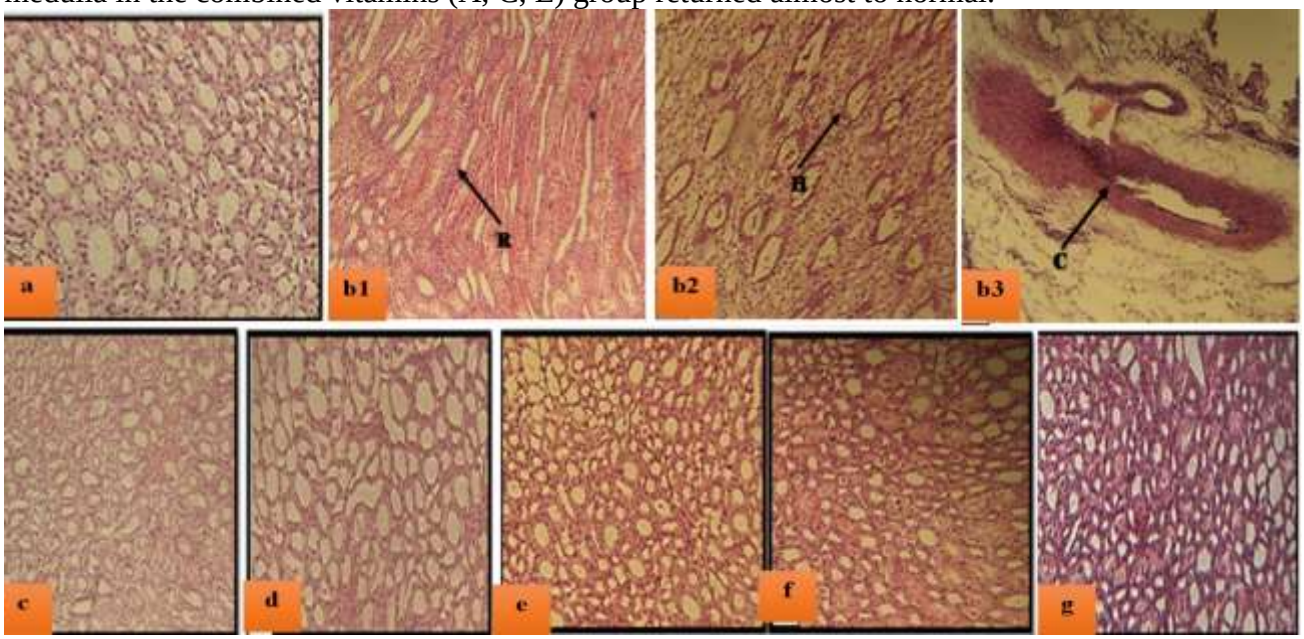

Fig. 2: (a) *Light micrographs of a cross-section in the kidney medulla of control guinea pigs showing normal histological structures of collecting tubules);* ***(b)*** *penicillin for 30 days, showing hyperplasia (H), compressed blood vessels (C) and hemorrhage (R);* ***(c):*** *Penicillin + S.honey;* ***(d):*** *Penicillin + vit A;* ***(e):*** *Penicillin + vit C;* ***(f):*** *Penicillin + vit E;* ***(g):*** *Penicillin + vit A, C&E showing most of the medulla return to normal histological structure. (H&E X 400).*

Figure 3: The kidney cortex of guinea pigs treated with streptomycin for 30 days displayed significant changes, such as glomerular shrinkage and thickened blood vessels, compared to the normal structure in controls. Co-treatment with Sidr honey or vitamins (A, C, and E) helped restore most of the cortical structure to normal.

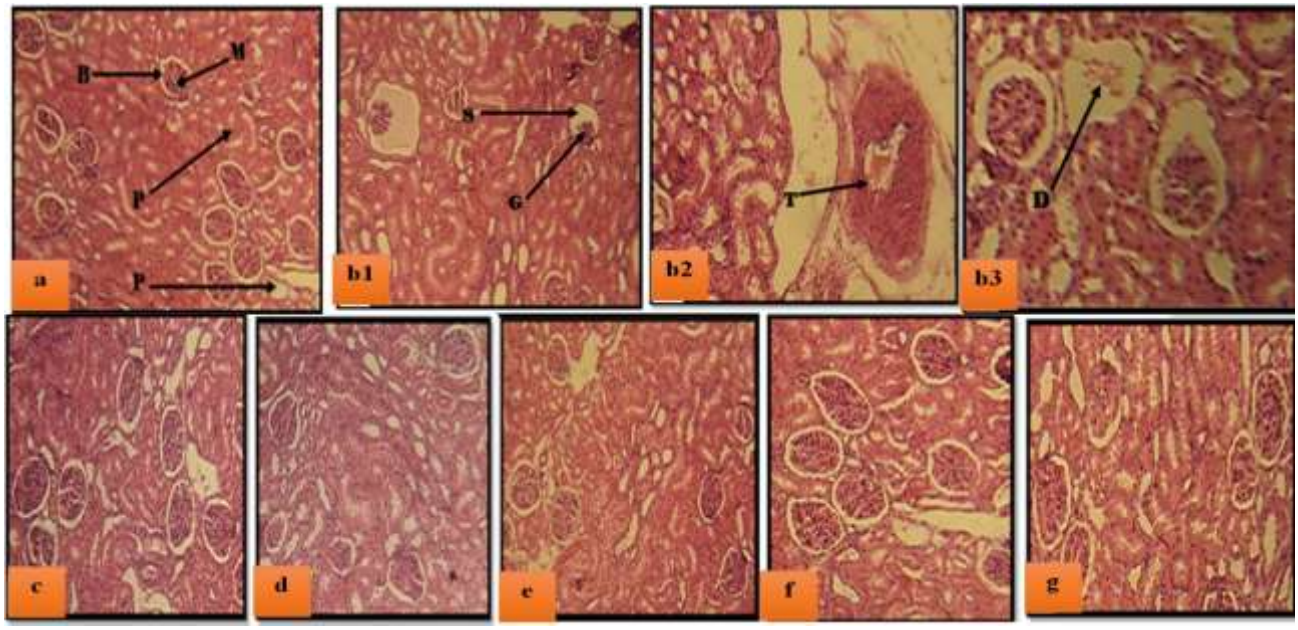

Fig. 3: (a) *Light micrographs of a cross-section in the kidney cortex of control guinea pigs showing normal histological structures of Malpighian corpuscles with its glomerulus (M) Bowman's capsule (B) proximal tubules (P) and distal tubule (D);* ***(b1,2,3):*** *streptomycin for 30 days showing dilatation of Bawmn's capsul (S), shrinkage glomerulus (G), glomerular degeneration (D), and thickened blood vessels (T);* ***(c):*** *Streptomycin + S.honey;* ***(d):*** *Streptomycin + vit A;* ***(e):*** *Streptomycin + vit C;* ***(f):*** *Streptomycin + vit E;* ***(g):*** *Streptomycin + vit A, C&E showing most of the cortex return to normal structure. (H&E X 400).*

Figure 4: Streptomycin treatment in the medulla led to noticeable damage, including medullary tubular casts, hyperplasia, and blood vessel compression. Sidr honey and vitamins (A, C, and E) treatments helped medullary structures return to near-normal, especially in the combined vitamin group.

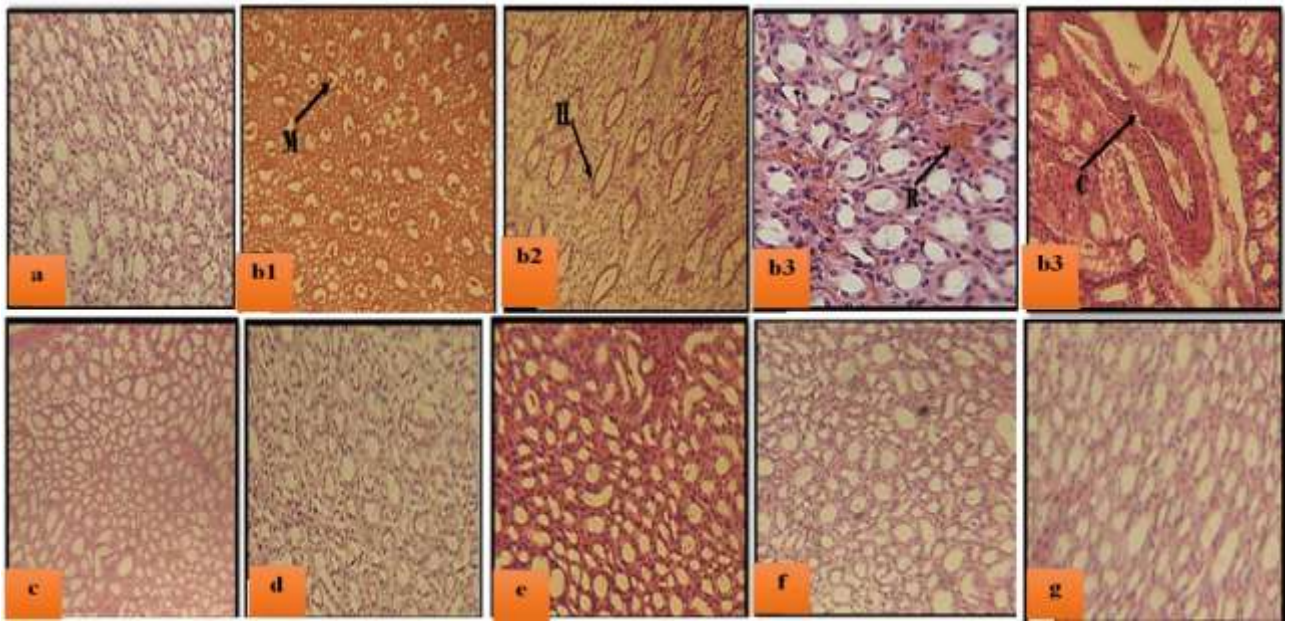

Fig. 4: (a) *Light micrographs of a cross-section in the kidney medulla of control guinea pigs showing normal histological structures of collecting tubules);* ***(b)*** *streptomycin for 30 days, showing medullary tubular casts (M), hyperplasia (H), compressed blood vessels (C) and hemorrhage (R);* ***(c):*** *Streptomycin + S.honey;* ***(d):*** *Streptomycin + vit A;* ***(e):*** *Streptomycin + vit C;* ***(f):*** *Streptomycin + vit E;* ***(g):*** *Streptomycin + vit A, C&E showing most of the medulla return to normal histological structure. (H&E X 400)*

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Figure 5: After 20 days of penicillin treatment, the kidney cortex exhibited abnormal structural changes like glomerular degeneration. Following penicillin withdrawal, treatments with Sidr honey and a combination of vitamins (A, C, and E) aided in restoring the cortex to its normal structure.

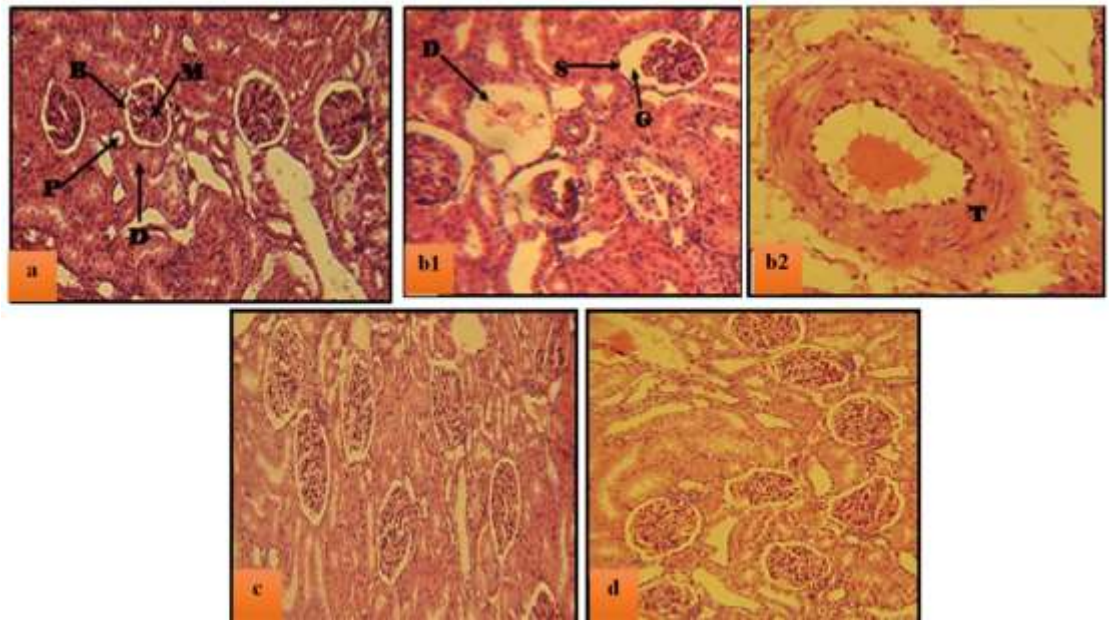

Fig. 5: *Light micrographs of a cross-section in the kidney cortex of guinea pigs.* ***(a):*** *control group showing normal histological structures of Malpighian corpuscles with its glomerulus (M) Bowman's capsule (B) proximal tubules (P) and distal tubule (D);* ***(b1,2):*** *Penicillin for 20 days showing dilatation of Bawmn's capsule (S), shrinkage glomerulus (G), glomerular degeneration (D), and thickened blood vessels (T);* ***(c,d)*** *Light micrographs of a cross sections in kidney cortex of guinea pig after administration of penicillin for 20 days, then* ***(c):*** *sidr honey for another 20 days;* ***(d)*** *vitamins A, C, E in combination for another 20 days, showing most of the cortex return to normal structure. (H&E X 400).*

Figure 6: In the medulla, penicillin-induced damage included tubular casts and hemorrhage after 20 days of administration. Treatments with Sidr honey or combined vitamins (A, C, E) following penicillin withdrawal improved structural integrity, returning the medulla to its original condition.

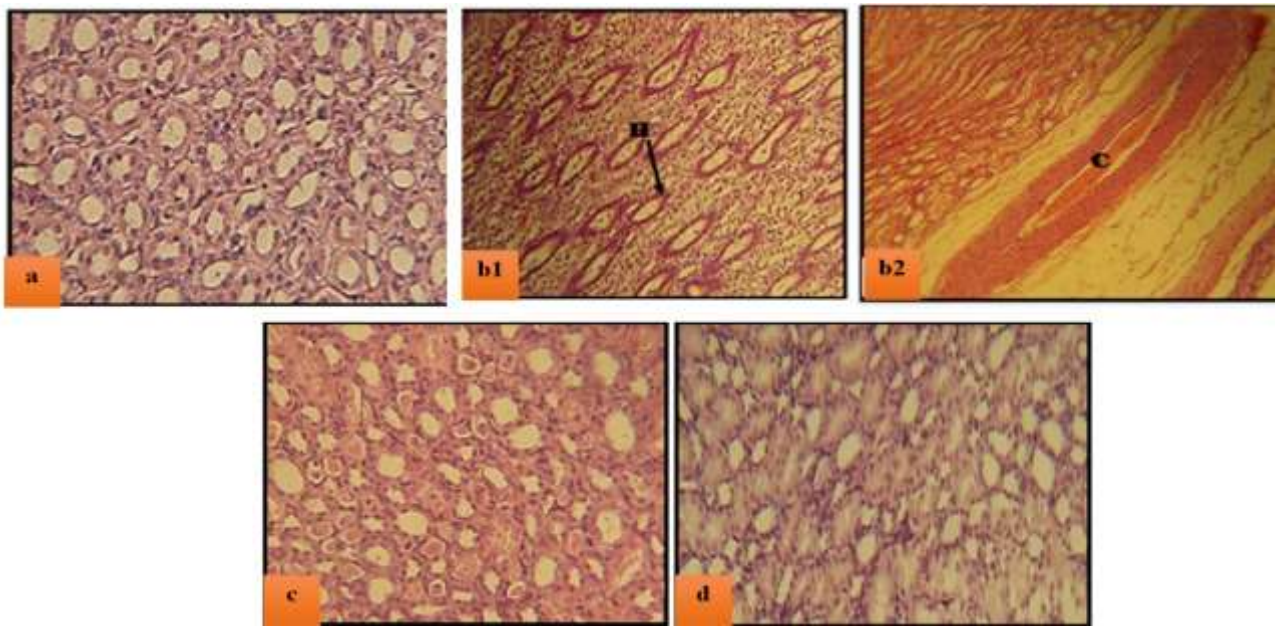

Fig. 6: *Light micrographs of a cross-section in the medulla of guinea pigs.* ***(a):*** *control group showing normal histological structures of collecting tubules.* ***(b1,2):*** *Penicillin for 20 days showing medullary tubular casts (M), hyperplasia (H), compressed blood vessels (C), and hemorrhage (R);* ***(c,d)*** *Light micrographs of a cross-section in kidney medulla of guinea pig after administration penicillin for 20 days, then* ***(c):*** *sidr honey for another 20 days;* ***(d)*** *vitamins A, C, E in combination for another 20 days, showing most of the medulla return to normal histological structure (Hx&E X 100).*

Figure 7: Guinea pigs treated with streptomycin for 20 days showed severe kidney cortex damage, which was visibly improved after 20 days of Sidr honey or vitamin combination treatment post-streptomycin withdrawal, with the cortex structure closely resembling normal tissue.

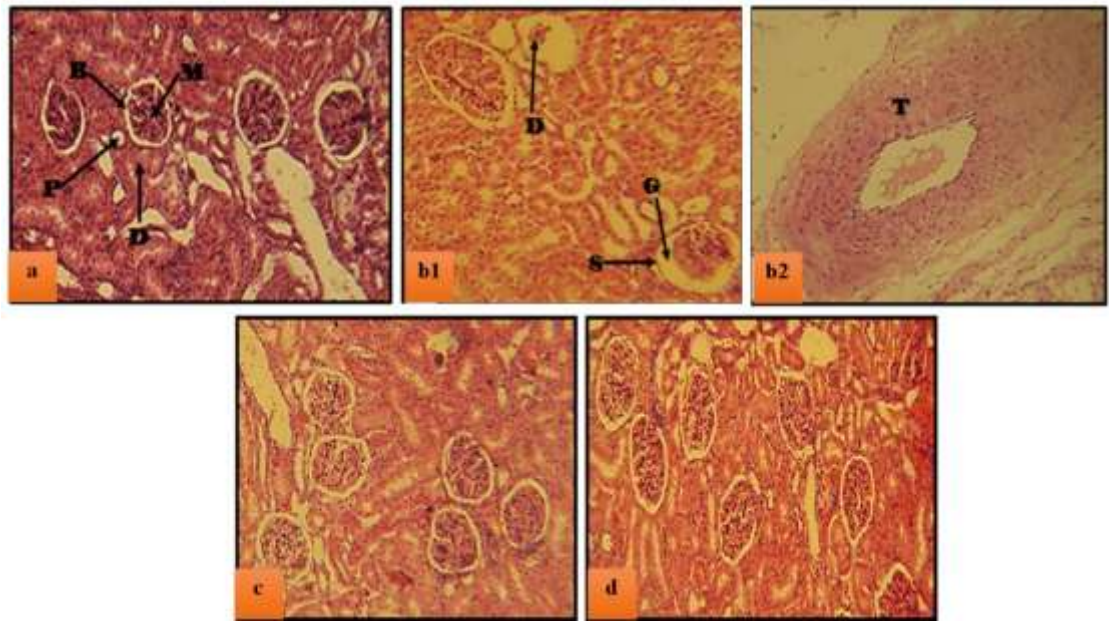

Fig. 7: *Light micrographs of a cross-section in the kidney cortex of guinea pigs.* ***(a):*** *control group showing normal histological structures of Malpighian corpuscles with its glomerulus (M) Bowman's capsule (B) proximal tubules (P) and distal tubule (D);* ***(b1,2)*** *Streptomycin for 20 days showing dilatation of Bawmn's capsule (S), shrinkage glomerulus (G), glomerular degeneration (D), and thickened blood vessels (T);* ***(c,d)*** *Light micrographs of a cross sections in kidney cortex of guinea pig after administration of streptomycin for 20 days, then* ***(c):*** *sidr honey for another 20 days;* ***(d)*** *vitamins A, C, E in combination for another 20 days, showing most of the cortex return to normal structure.*

Figure 8: Streptomycin treatment caused notable damage in the kidney medulla, but post-treatment with Sidr honey or combined vitamins (A, C, E) facilitated a return to normal histology.

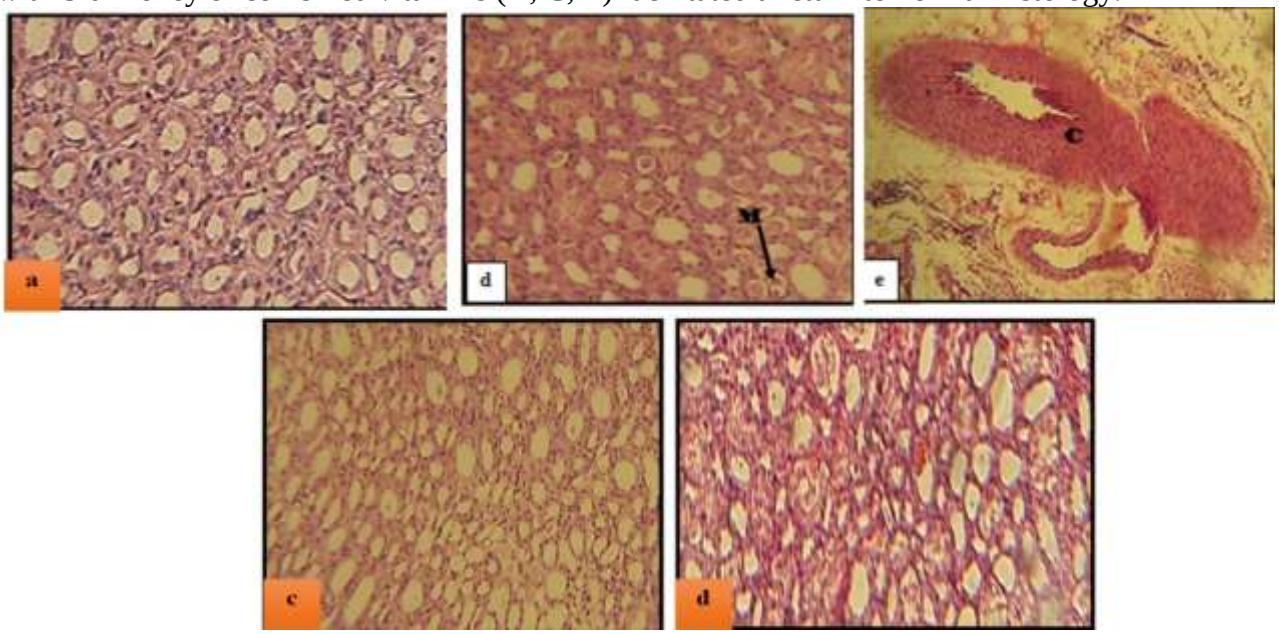

Fig. 8: *Light micrographs of a cross-section in the medulla of guinea pigs.* ***(a):*** *control group showing normal histological structures of collecting tubules.* ***(b & c)*** *Streptomycin for 20 showing medullary tubular casts (M), hyperplasia (H), compressed blood vessels (C), and hemorrhage (R);* ***(c,d)*** *Light micrographs of a cross-section in kidney medulla of guinea pig after administration Streptomycin for 20 days, then* ***(c):*** *sidr honey for another 20 days;* ***(d)*** *vitamins A, C, E in combination for another 20 days, showing most of the medulla return to normal histological structure (Hx&E X 100).*

4. Discussion

The kidneys are critical for excreting toxins in mammals but are highly susceptible to damage from various drugs and chemicals [15,16]. This study demonstrated that the administration of penicillin or streptomycin to guinea pigs significantly increased serum levels of urea, creatinine, and uric acid, reflecting impaired renal function and kidney stress. Histological examination confirmed these findings, showing marked renal tissue damage such as glomerular shrinkage, tubular degeneration, and hemorrhage. This damage may arise from antibiotic accumulation in the renal tubular cells, producing reactive oxygen species (ROS) and oxidative stress, which disrupt renal filtration and cellular function [4,5,17,18].

In this study, Sidr honey and vitamins A, C, and E were examined as preventive (cotreatment) and curative (post-treatment) agents against renal toxicity induced by penicillin and streptomycin.

In the preventive group, Sidr honey and vitamins were administered concurrently with antibiotics to mitigate potential renal damage. Tables 1 and 2 show that co-treatment with Sidr honey (G3, G9) and vitamins (G4-G6, G10-G12) reduced the increases in urea, uric acid, and creatinine levels caused by penicillin or streptomycin, indicating improved renal function. The combined vitamin treatment (G7, G13) was especially effective in restoring kidney markers closer to the control levels. This suggests that when administered with antibiotics, antioxidants neutralize the free radicals generated during antibiotic metabolism, reduce oxidative stress, and protect renal cells, particularly in the cortex and medulla [7-12, 19,20].

Histological results also support these findings. In the penicillin-treated groups, co-treatment with Sidr honey or vitamins helped maintain the kidney structure and reduced glomerular and tubular degeneration. A similar protective effect was observed in streptomycin-treated groups, with reduced hyperplasia, vascular dilation, and other structural abnormalities in groups receiving antioxidants [5,21-24]. This aligns with previous studies in which antioxidants have been shown to prevent renal damage by mitigating cellular oxidative damage caused by antibiotics [25,26].

In the curative groups, antioxidants were administered after 20 days of penicillin or streptomycin treatment to assess their ability to reverse the established renal damage. Table 3 shows that post-treatment with Sidr honey (G16, G19) or combined vitamins (G17, G20) significantly lowered serum urea, uric acid, and creatinine levels compared to the untreated antibiotic groups, although levels did not fully normalize. This suggests that antioxidants facilitate cellular repair, aiding the recovery of renal function following toxic exposure [28-29].

Histologically, curative treatment with Sidr honey and vitamins resulted in notable improvements in kidney structure, with many renal corpuscles and tubules appearing close to normal. Combined vitamin treatment appeared particularly effective in reversing glomerular and tubular degeneration as well as medullary damage. This suggests that antioxidants enhance cellular detoxification pathways, help clear residual toxins, and promote tissue repair [28,30].

The nephroprotective effects of Sidr honey and vitamins A, C, and E likely stem from their antioxidant properties, which counteract ROS and support renal health. Sidr honey contains phenolic compounds that effectively scavenge free radicals, whereas vitamins stabilize cellular membranes, enhance immune defenses, and support tissue regeneration. The combined use of these antioxidants appears to offer a strong defense against renal toxicity, as evidenced by significant reductions in biochemical markers and histological damage [30,31].

Antioxidants may reduce the formation of ROS during antibiotic metabolism, limiting the initial oxidative stress on the renal tissue. Curatively, they likely aid in cellular recovery by eliminating residual toxins, enhancing renal filtration, and supporting the regeneration of damaged cells [29,30]. This dual action in both prevention and repair aligns with previous research on the role of antioxidants in countering antibiotic-induced nephrotoxicity [30,31,35].

Conclusion

In summary, this study highlights the beneficial roles of Sidr honey and vitamins A, C, and E in protecting and restoring renal function following exposure to penicillin and streptomycin. When used

as co-treatments or post-treatments, these antioxidants significantly reduced the biochemical and structural indicators of kidney damage. Their potential as adjunctive therapies to manage drug-induced nephrotoxicity warrants further investigation, especially in clinical settings, where kidney health must be safeguarded.

5. References

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