Effect of Praziquantel, Allicin, and Curcumin on The Histology of Liver, Spleen, and Kidney of Schistosoma mansoni Infected Mice

Original Article

Ali Hussein Abu Almaaty[1], Hadeer Abd El-Hak Rashed[1], Maha Farid Mohamed Soliman[2] and Nahla Soliman El-Shenawy[2]

Department of Zoology, Faculty of Science, [1]Port Said University, Port Said, [2]Suez Canal University, Ismailia, Egypt

ABSTRACT

Background: Human schistosomiasis was considered a tropical disease causing histological deformation in different organs.
Aim of the Work: To focus on the possible therapeutic efficiency of praziquantel (PZQ), allicin (AL), and curcumin (CU) in healing the histopathological disorders in Schistosoma mansoni infected mice.
Material and Methods: Ninety mice were divided into two main groups; uninfected and infected groups. From the 7th week, post-infection, the groups begin their treatment with the different regimens. PZQ (300 mg/kg) groups were given the drug orally for two successive days. The groups of AL (40 mL/kg) or CU (40 mg/kg) were given by intraperitoneal injection for two weeks. The histological changes of the liver, spleen, and kidney were recorded to determine the effect of each treatment.
Results: AL and CU were able to ameliorate these histopathological lesions resulted from infection competitively with PZQ. In the liver, the highest reduction rate in granuloma number was recorded in the infected mice treated with CU while the highest reduction rate in granuloma diameter was recorded in the PZQ-treated group. The infected groups treated with PZQ or AL showed mild alternation in splenic structures. The most ameliorative healing effect was noticed in the infected mice treated with CU as there were no lesions recorded in spleen tissue. The all tested elements caused lesions in both the non-infected and the infected animals.
Conclusion: This promising research suggests the potential efficacy of AL, and CU in ameliorating the histopathological effects of schistosomiasis, in a competitive manner with PZQ. We recommended for further investigations to use AL and CU as complementary drugs with PZQ and to study the effect these drugs on different organs' functions based on the biochemical tests.

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Key Words: Allicin, curcumin, histopathology, praziquantel, schistosomiasis.

Corresponding Author: Hadeer Abd El-Hak Rashed, PhD, Department of Zoology, Faculty of Science, Port Said University, Port Said, Egypt, **Tel.**: +20 1069869539, **E-mail:** hader_abdelhak@hotmail.com

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INTRODUCTION

Schistosomiasis is a disorder caused by parasitic worms. It is considered a neglected tropical disease by the World Health Organization[1]. Schistosoma mansoni is one of the etiological factors of human schistosomiasis that is endemic in Africa, the Middle East, the Caribbean, and South America[2]. Schistosoma infection is the third most destructive tropical disorder in the world and resulted in significant morbidity and mortality on many continents[3].

The host immune cell T-helper 2 response against S. mansoni eggs resulted in granuloma formation in the infected-tissue followed by collagen deposition and finally fibrosis[4]. Granuloma diameter and number are still used as a tool of treatment qualification by many authors[5,6].

Schistosomiasis caused deformation of hepatic lobules, degradation of hepatic cords, degeneration and necrosis of hepatocytes. These changes could be due to granuloma formation, hypertrophy of Kupffer cells. Marked depletion of carbohydrates and increased lipid vacuoles can be also observed[7,8]. Also, S. mansoni infections resulted in histological deformations in the other different organs such as intestine, kidney, spleen, and lungs[9,10,11].

Histopathologic scoring is a method used to get semi-quantitative data of lesions in different tissue structures[12]. Microscopic histopathological examination is still one of the most common methods of scoring used by investigators[13,14].

The long-term worldwide use of praziquantel (PZQ), the only drug of choice, resulted in the discovery of PZQ-tolerant schistosomes which had induced concern over the development of drug-resistant Schistosoma strains[15].

Allicin (AL), the principal bioactive ingredient of Allium sativum, is considered mainly as an alkaloid that suggested being responsible for useful characteristics of garlic[16]. AL has been reported by previous investigators to have antitumor, antioxidant, anti-inflammatory, and antischistosomal effect[17,18,19].

Curcumin (CU) is a highly yellow pigment produced from rhizomatous plant turmeric (Curcuma longa) widely produced in tropical and subtropical areas all

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over the world[20]. C. longa crude was reported to have an antischistosomal effect[21]. Investigators found that CU has different beneficial therapeutic properties[22,23,24].

AIM OF THE WORK

This study aimed to evaluate the potential efficacy of PZQ, Al, and CU on the histological structures of liver, kidney, and spleen of S. mansoni infected mice.

MATERIAL AND METHODS

Chemicals

Praziquantel was brought from the Egyptian international pharmaceutical industries company (EIPICO). Liquid allicin (AL; C6H10OS2) was purchased from Science Med., Egypt, and then diluted in distilled water to get the desired concentration. A vial of curcumin powder (CU; C21H20O6) was obtained from Sigma Aldrich and was dissolved in phosphate buffer (PB; PH 7.2).

Experimental animals

Ninety CD1 male albino mice ranging from (18-26 g) were brought from Theodore Bilharz Research Institute (TBRI), Egypt. They were placed in cages, 10 mice per cage, and kept in Zoology Department Animal House, Faculty of Science, Port-Said University. They are kept under the standard conditions at room temperature (20 - 25 °C), with exposure to 12 h light / dark cycle and had free access to pellet food with tap water ad libitum. Mice were observed daily, and only healthy animals were used in this experiment.

Experimental design

The mice were divided into two main groups (uninfected and infected) that were subdivided into subgroups.

1. Uninfected subgroups

All the mice were clear uninfected and treated at the beginning of the 7th week of housing. These subgroups included 50 mice (10 mice per subgroup) as follows:

Subgroup 1a (-ve control): mice of this group were left without intervention.

Subgroup 1b (Saline group): mice were injected IP with 0.1 mL/mouse of 0.9% NaCl using insulin syringe.

Subgroup 1c (PZQ): animals were orally treated with 0.1 mL/ mouse of the PZQ (600 mg/kg body weight) divided into two equal doses of 300 mg/kg given in two successive days using gastric tube.

Subgroup 1d (AL): animals were injected IP with 0.1 mL/ mouse of AL (40 mg/kg body weight) using insulin syringe.

Group 1e (CU): negative uninfected mice were injected with 0.1 mL/mouse of CU (40 mg/kg body weight) using insulin syringe. All the treatments with exception to the PZQ subgroup were carried out for two weeks on each alternative day.

2. Infected subgroups

The animals were infected subcutaneously with 60±10 S. mansoni cercariae (infective stage) suspended in normal saline. These subgroup included 40 mice (10 mice per subgroup). Seven weeks post-infection, mice were treated with the tested ingredients as follows:

Subgroup 2a (infected-untreated group): mice of this group were left without intervention.

Subgroup 2b (Infected + PZQ): animals were orally treated with 0.1 mL /mouse of PZQ (600 mg/kg body weight) divided into 2 equal doses of 300 mg/kg given in two successive days using gastric tube.

Subgroup 2c (Infected + AL): infected mice were injected IP with 0.1 mL/mouse of AL (40 mL/kg body weight) using insulin syringe.

Subgroup 2d (Infected + CU): infected mice were injected IP with 0.1 mL of CU (40 mg /kg body weight) using insulin syringe.

AS like as uninfected sub-groups, all the treatments with exception to the PZQ group were carried out for two weeks on each alternative day. The dose of the treatment with PZQ (non-infected and infected) was according to Chaiworaporn *et al*.[25]. The doses of Al and CU were selected based on the preliminary study on the effect of different doses of AL (10, 20, and 40 mL/kg body weight) and CU (10, 20, and 40 mg/kg body weight) on the mice. We found that the highest doses were the most effective in the worm burden rates and thus were used in the experimental animal design of the present study.

Histopathological study

Specimens of liver, spleen, and kidney were immediately removed out from dissected animals under anesthesia, fixed in 10% buffered formalin, embedded in paraffin. Sections of 4 µm thickness were obtained from the prepared blocks and then stained with hematoxylin and eosin. The (H&E) stained sections were observed and then scored under the light microscope. Scoring was used to compare the structural changes and the histopathological disorders in the tissue sections of the different groups. Lesions were graded from - (no lesions) to +++ (severe lesion in > 6 mice)[26].

Morphometric study

Three liver paraffin sections (4 µm) from each animal of the infected groups were prepared and then stained with hematoxylin and eosin. The section was 250 µm apart from the previous ones to prevent the measuring of the same granuloma. Only granulomas having a central eggs were measured. Each granuloma mean diameter (µm) was obtained through measuring two diameters of each one at right angles to each other using CMEX (10 pros) software. Seventy granuloma of each group were measured and calculated[27].

Mean diameter of each granuloma (µm) = Sum of the two diameters of the lesion / 2.

For the counting process of the granuloma number, twenty fields were analyzed using a light microscope. The mean granulomas number was calculated in 100 mm2/ group[28].

Ethics

Anesthetic procedures complied with the ethical guidelines approved by the Ethical Committee of the Federal Legislation and National Institute of Health Guidelines in USA were approved by the Medical Ethical Committee of Theodore Bilharz Research Institute (TBRI) in Egypt.

Statistical analysis

Granulomas measurements were expressed as the mean ± standard error (S.E.). The analysis of variance (ANOVA) followed by the post-hoc test was done using Statistic Program Sigma Stat (SPSS), version 20. Comparing the infected-untreated and the infected-treated groups was carried out to show the therapeutic effect of PZQ, AL, and CU. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Liver

1. Uninfected control groups

In the uninfected mice of all subgroups, the hepatocytes were acidophilic and contained central pale stained nuclei. The hepatocyte cords are separated by blood sinusoids that reveal sinusoid-associated resident macrophages which known as Kupffer cells (Figures 1A-1E). However, in the CU group, there was a mild leaking of the inflammatory cells out of the blood vessels, and this condition is known as cellular infiltration (Table 1 and Figure 1E).

2. Infected groups

There were severe disorders (+++) as inflammatory cellular infiltration, fibers surrounding some granulomas, and damaged hepatocytes (highly stained) that changed into vacuolated regions in the infected-untreated mice (Table 1 and Figures 2A-2B). In the infected treated sub-groups, no changes (+++) was observed in all treated groups in cellular infiltration conditions (Table 1 and Figures 2C-2F). The best amelioration in the rest lesions was obseved in the CU group as there was mild (+) lesions (Table 1 and Figure 2G). Granuloma

The areas of liver section suffering from granuloma in the infected groups are shown in (Figures 2B,2D,2F,2H). We noticed a central Schistosoma egg surrounded by infiltrated immunological cells, and fibers. There was a significant reduction ($P < 0.00$) in granuloma number in the infected groups treated with PZQ or AL or CU as compared to the infected-untreated animals. The highest reduction rate (56.80%) in granuloma number was recorded in CU-treated mice in comparison with the infected-untreated group. The average diameter of granulomas in the infected untreated liver was 467.27 ± 37.43. All the infected treated groups showed a significant decrease in the granuloma diameter as compared to the infected-untreated group. The lowest granulomas average diameter was recorded in mice treated with PZQ (330.58 ± 19.91) ($P< 0.002$) with a reduced rate of 29.25% (Table 2).

Spleen

1. Uninfected control groups

The microscopic sections of the spleen in the uninfected treated subgroups were approximately the same without basic structural differences between them. The spleen architecture was composed mainly of red and white pulps. In the red pulp, there were blood sinusoids, while in the white pulp there was a central arteriole surrounded by cells. There were no remarkable pathological changes in the spleen architecture of the different uninfected treated animals (Table 1 and Figure 3).

2. Infected groups

The pathological disorders recorded in the infected untreated mice were severe and included vasodilatation of blood sinusoids and splenic foci (Table 1 and Figures 4A-4B). The infected groups treated with PZQ or AL showed no (-) vasodilatation and mild changes (+) in splenic foci (Table 1 and Figure 4C-4F). The best result recorded for the infected mice treated with CU because there were no recorded lesions (Table 1 and Figures 4G-4H).

Kidney

1. Uninfected control groups

The pathological disorders in the kidney sections scored in the uninfected and the infected groups treated with (PZQ or AL or CU) (Table 1). This effect in the uninfected groups was restricted to kidney tissues. However, both liver and spleen sections discussed previously did not reflect pathological changes in the un-infected animals. The recorded histopathological disorders included hemorrhage, tubular damage, and glomerular atrophy.

The microscopic sections and scoring of the kidney in the uninfected groups either saline or –ve control group reflected approximately tissue without remarkable changes (Table 1 and Figures 5A-5B). The renal cortex was composed of several renal glomeruli that were surrounded by the proximal and the distal convoluted tubules. Glomerulus was a bundle of winding capillaries surrounded by Bowman capsule. There were mild hemorrhage and glomerular atrophy (+) in the un-infected animals treated with (PZQ or AL or CU) (Table 1 and Figures 5C-5E).

2. Infected groups

Beside hemorrhage and glomerular atrophy recorded in the infected-untreated groups, there was also tubular damage (Table 1 and Figure 6A). There was an improvement in the structure of the kidney in the infected mice treated with (PZQ or AL or CU) in comparison with the infected-untreated mice (Figures 6B-6D). The infected group treated with CU recorded the best amelioration as there was only mild glomerular atrophy (+) (Table 1 and Figure 6D).

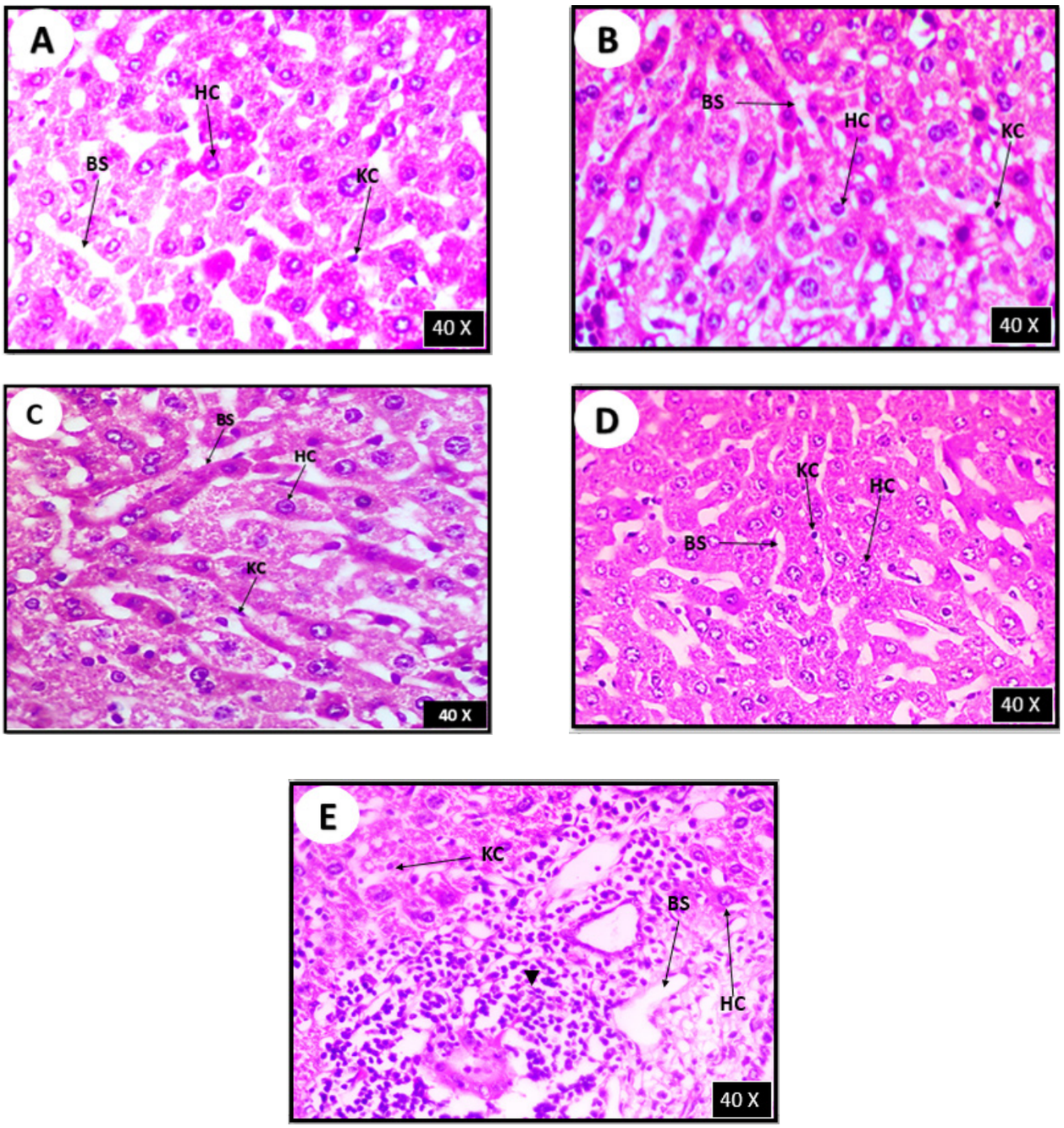

Fig. 1: Liver sections of un-infected groups. –ve group (A). Saline group (B). PZQ group (C). AL group (D). CU group (E). HC; hepatocytes, BS; blood sinusoids, KC; Kupffer cells, Black arrowhead; cellular infiltration. H&E.

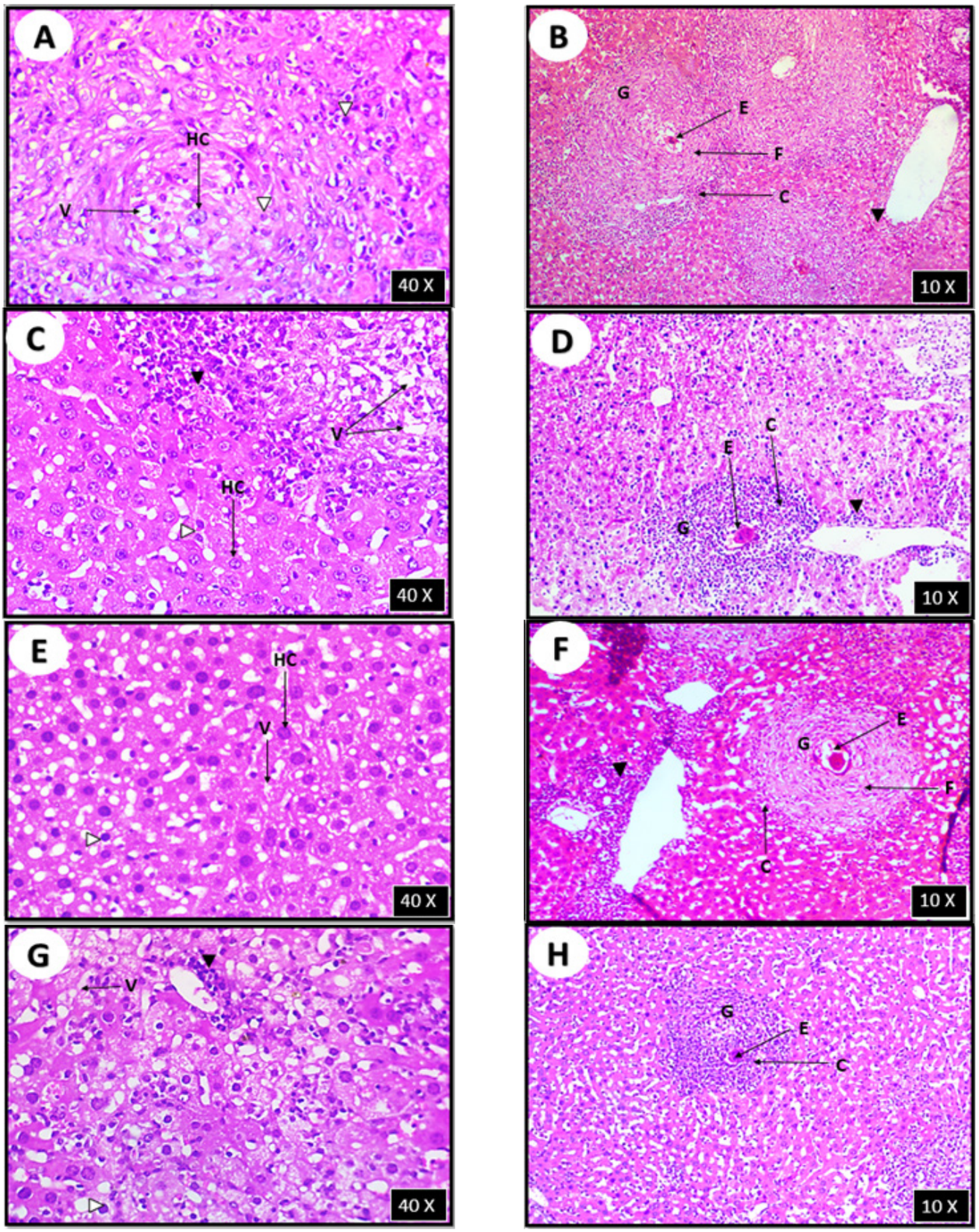

Fig. 2: Liver sections of infected groups. Infected untreated group (A-B). Infected + PZQ group (C-D). Infected + AL group (E-F). Infected + CU group (G-H). G; Granuoma (E; egg, C; cells, F; fibers), HC; hepatocytes, V; vacuolation, Black arrowhead; cellular infiltration, White arrowhead; damaged hepatocytes. H&E.

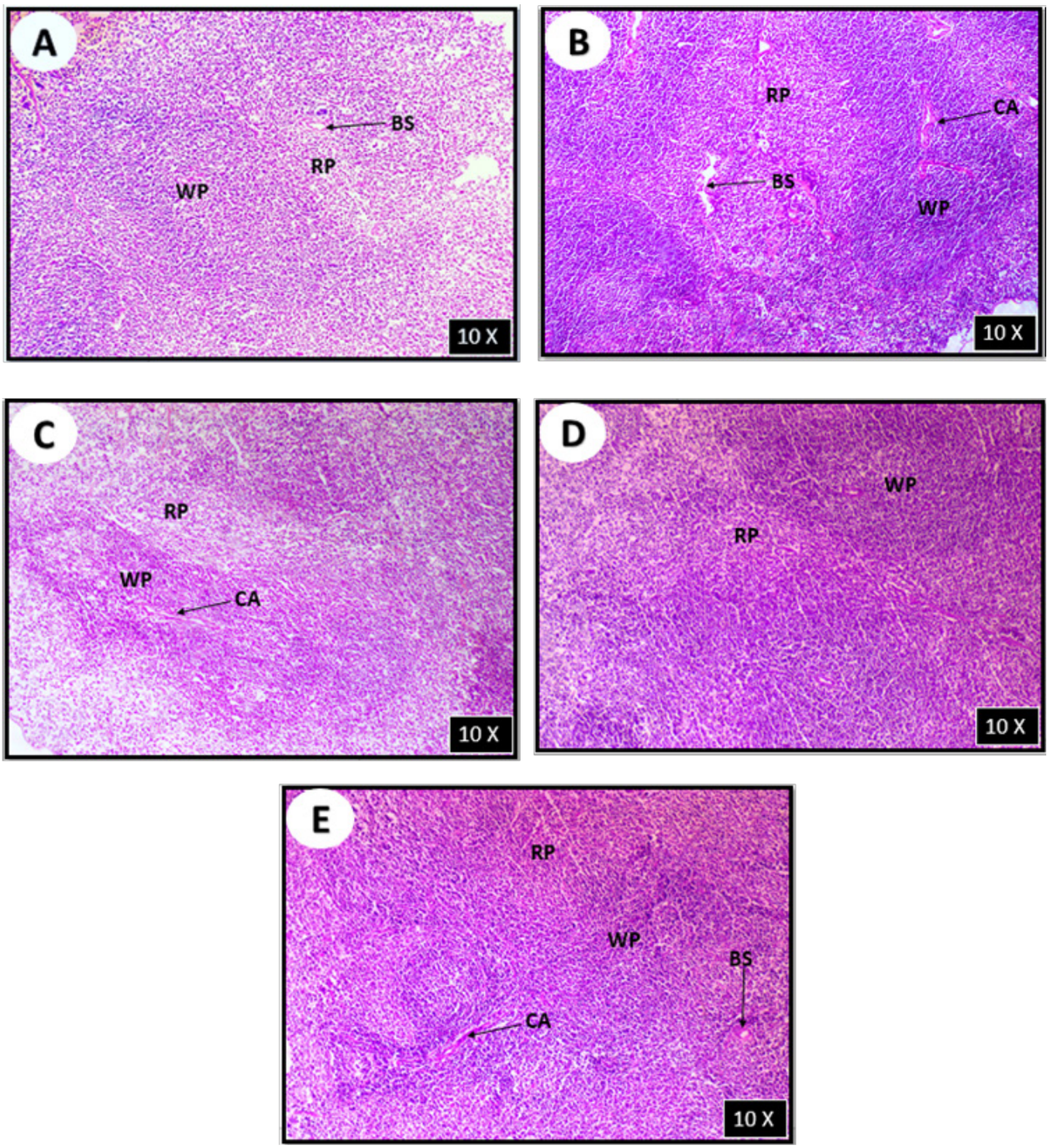

Fig. 3: Spleen sections of un-infected groups. –ve group (A). Saline group (B). PZQ group (C). AL group (D). CU group (E). RP; red pulp, WP; white pulp, CA; central arteriole, BS; blood sinusoids. H&E.

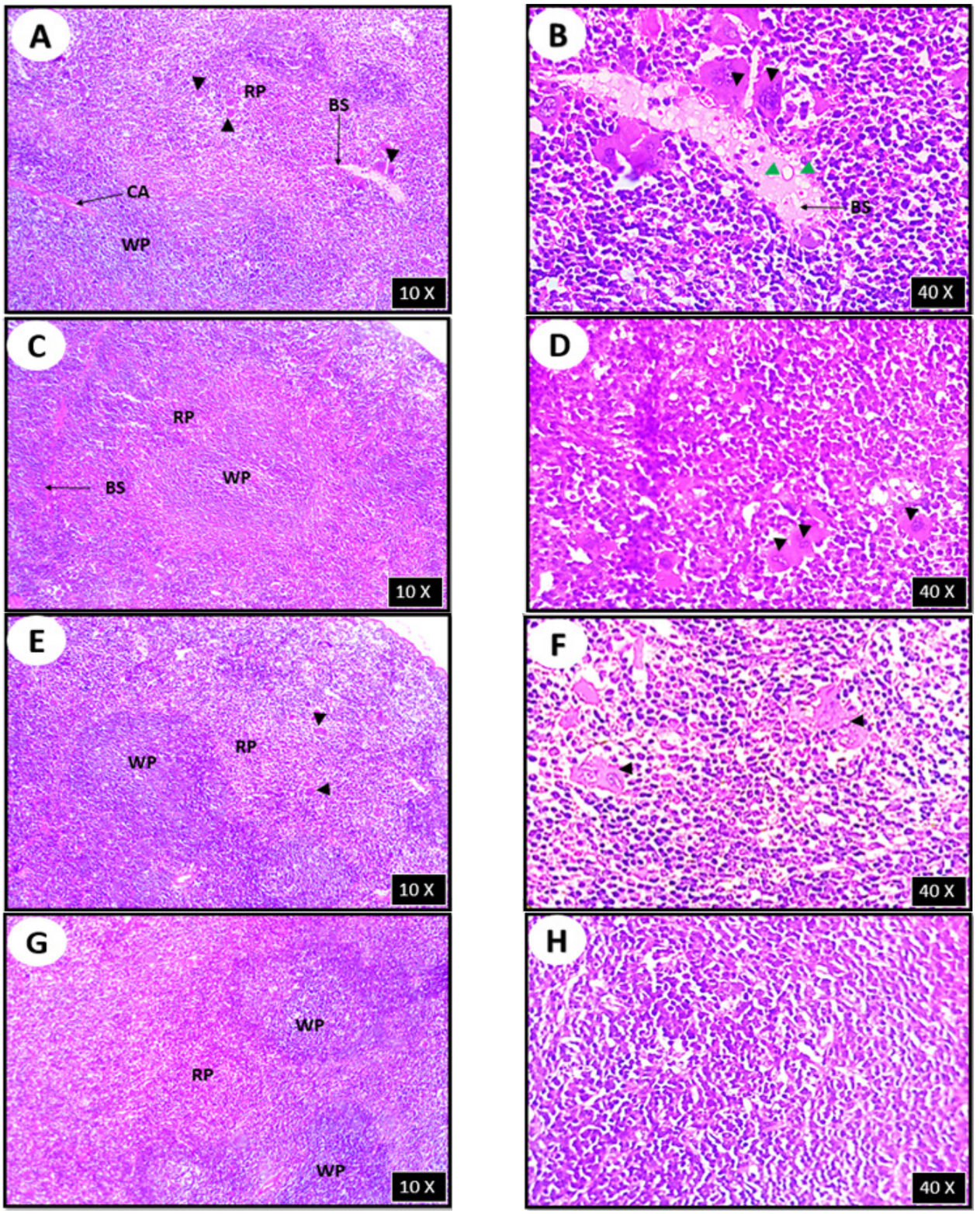

Fig.4: Spleen sections of infected groups. Infected untreated group (A-B). Infected + PZQ group (C-D). Infected + AL group (E-F). Infected + CU group (G-H). RP; red pulp, WP; white pulp, CA; central arteriole, BS; blood sinusoids, Green arrowhead; vasodilation in blood sinusoids, Black arrowhead; splenic foci. H&E.

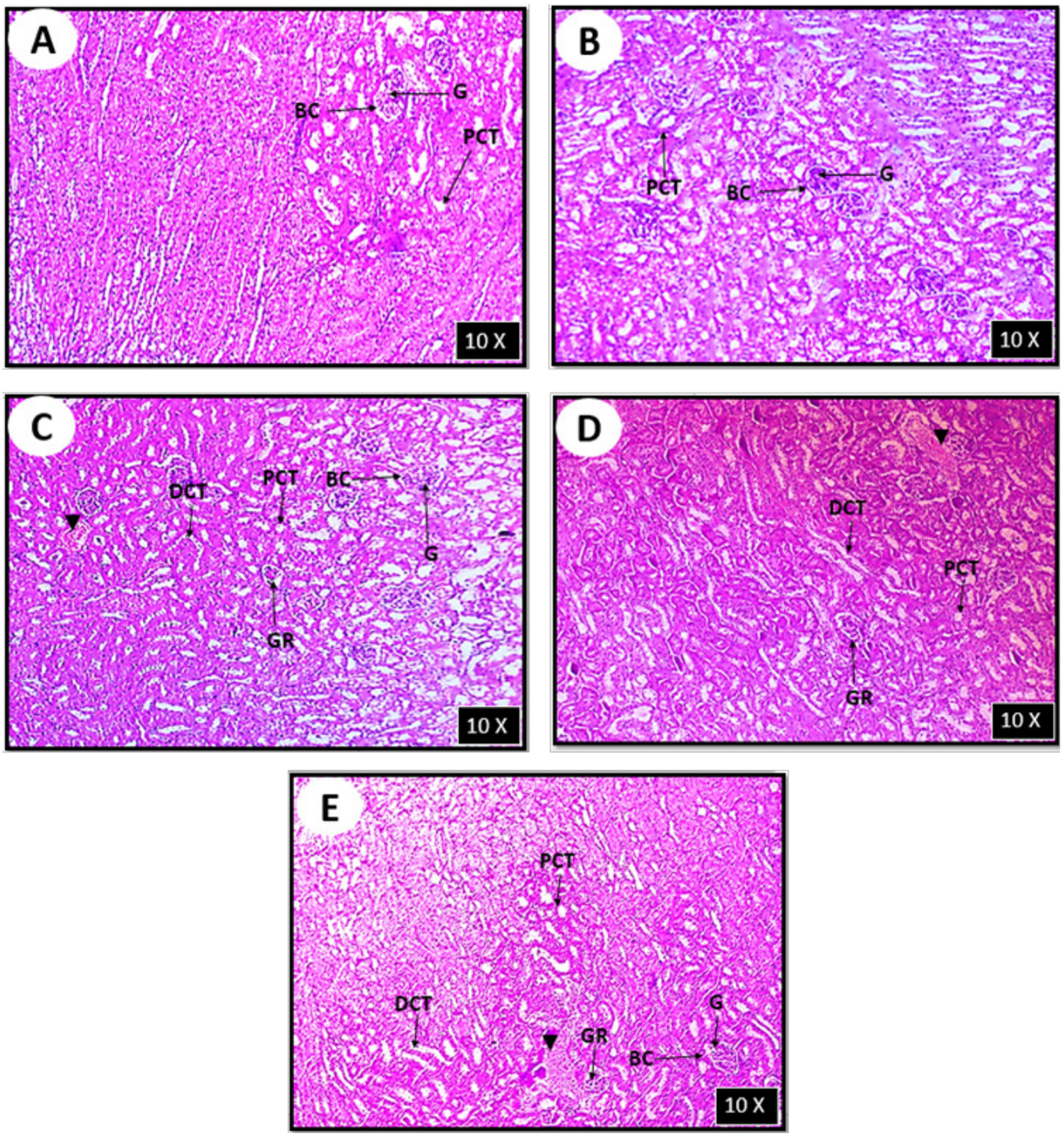

Fig. 5: Kidney sections of un-infected groups. –ve group (A). Saline group (B). PZQ group (C). AL group (D). CU group (E). G; glomerulus, BC; Bowman's capsule, PCT; proximal convoluted tubules, DCT; distal convoluted tubules, GR; glomerular atrophy, black arrowhead; hemorrhage. H&E.

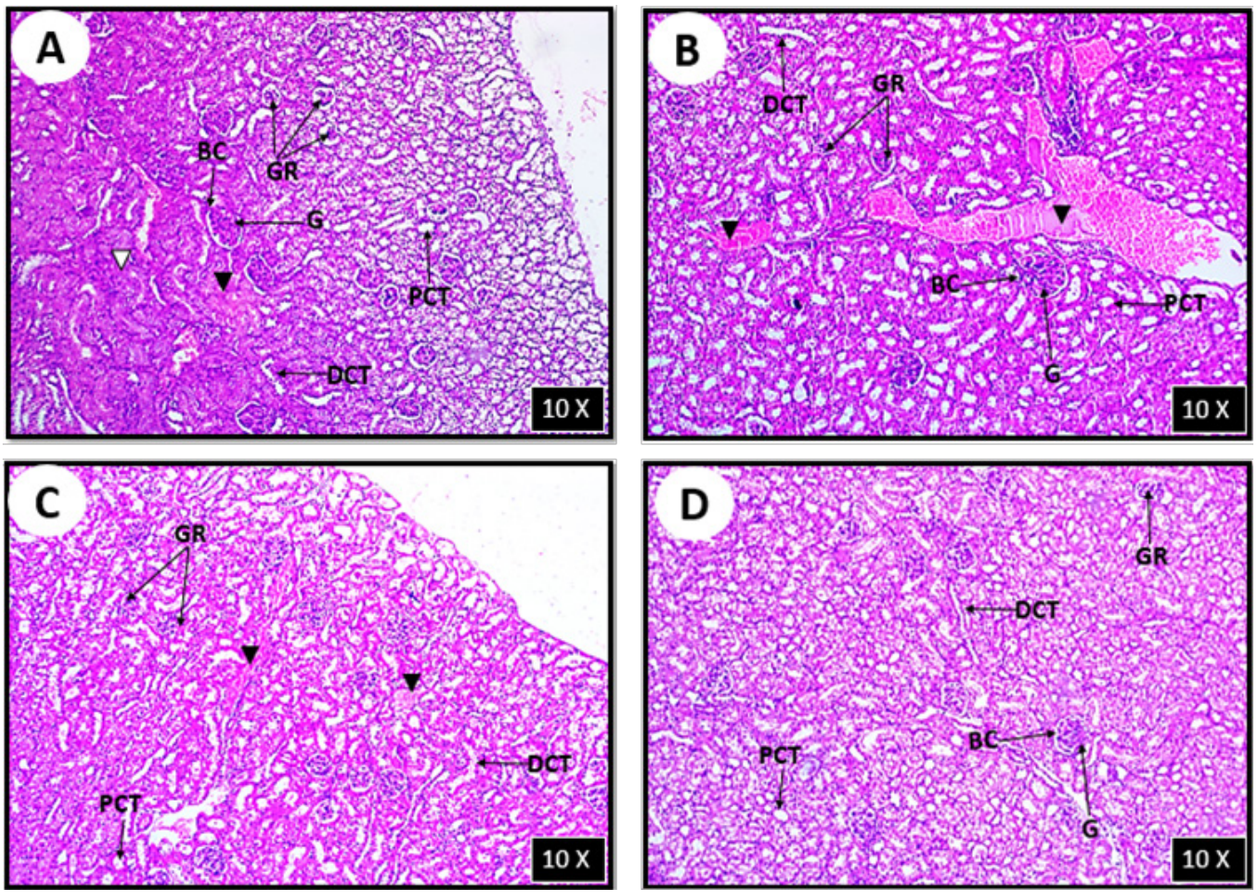

Fig. 6: Kidney sections of infected groups. Infected untreated group (A). Infected + PZQ group (B). Infected + AL group (C). Infected + CU group (D). G; glomerulus, BC; Bowman's capsule, PCT; proximal convoluted tubules, DCT; distal convoluted tubules, GR; glomerular atrophy, black arrowhead; hemorrhage, White arrowhead; tubular deformations. H&E.

Table 1: Histopathological lesions scoring in mice after different treatment regimens

Groups	Liver				Spleen		Kidney		
	Cellular infiltration	Fibers accumulation	Hepatocytes damage	Vacuolated areas	Vaso-dialation	Splenic foci	Hemorrhage	Tubular deformations	Glomerular atrophy
-ve control	-	-	-	-	-	-	-	-	-
Saline	-	-	-	-	-	-	-	-	-
PZQ	-	-	-	-	-	-	+	-	+
AL	-	-	-	-	-	-	+	-	+
CU	+	-	-	-	-	-	+	-	+
Infected untreated	+++	+++	+++	+++	+++	+++	+++	++	++
Infected + PZQ	+++	++	+	+	-	+	++	-	+
Infected + AL	+++	++	++	++	-	+	+	-	+
Infected + CU	+++	+	+	+	-	-	-	-	+

(-); null lesions, (+); lesion in 1-3 mice, (++); lesion in 4-6 mice, (+++); lesion in > 6 mice.

Table 2: Mean granuloma number and diameter with reduction rate in infected mice after different treatment regimens

	Granuloma number		Granuloma diameter (µm)	
	Mean	% reduction	Mean	% reduction
Infected untreated	28.17 ± 1.01	-	467.27 ± 37.43	-
Infected + PZQ	13 ± 1.61 c	53.85	330.58 ± 19.91 c	29.25
Infected + AL	13.33 ± 1.74 c	52.66	381.31 ± 13.98 c	18.40
Infected + CU	12.17 ± 1.38 c	56.80	331.91 ± 20.98 c	28.97

Values are presented as mean ± SE. c significant difference from the infected untreated group.

DISCUSSION

This study was focusing on the histopathological alternations in liver, spleen, and kidney of schistosomiasis mansoni infected mice. Introducing Al and CU as antischistosomal drugs was an attempt to search for a complementary treatment beside PZQ.

Regarding the liver tissues in the uninfected-groups, there were no histological changes between most sub-groups. There was an exception to the CU group as there was a cellular infiltration in some areas. This cellular infiltration may be due to changes in the vascular permeability as curcumin increases the blood flow as reported by previous authors[29]. CU-group result runs against previous studies[30,31], and this may be due to some differences in the dose of treatment, using an active ingredient or the plant itself or even the method of treatment-orally or intraperitoneally (IP).

The liver sections of the infected-untreated mice had cellular infiltration, fibers accumulation, and general damage as well as vacuolation. These changes were in agreement with previous studies[7,8]. There was no remarkable difference between the infected-untreated group and those infected and treated with PZQ or AL or CU as regards cellular infiltration conditions. The cellular infiltration was expected as the interstitial leaking of immune cells out of blood vessels is correlated with granuloma formation as reported by previous investigators[7,19]. Also, in the present study, granuloma was formed in the all infected groups either treated or not. Comparing the attenuation of the histopathological changes in liver sections of the infected-treated groups, the CU group showed the best result, followed by PZQ and finally AL. Al and CU as bioactive components resulted in healing of damaged liver tissues, and increasing the number of intact hepatocytes as reported by previous authors[32,33].

In the present study, the reduction of granuloma number and diameter in the PZQ-treated group was 53.85%, and 29.25%, respectively. PZQ results were close to a previous study[6] as the number of granulomas decreased to 60.67%, and their diameter diminished to 19.9%. In AL treated animals, the reduction rates of granuloma number and diameter were 52.66% and 18.40%, respectively. AL decreased the fibro-cellular granuloma diameter due to its anti-inflammatory effect[19]. The reduction rates of granuloma number and diameter in mice received turmeric were 29.4% and 43.1%, respectively as reported in a previous study[34]. In the present results, the CU group showed different reduction rates of granuloma number and diameter (56.80 % and 28.97%, respectively). The difference in the current results of CU from the previous study could be due to some factors as using the active ingredient and not the C. longa plant extract. Also, the period of treatment and the doses were different in both studies.

S. mansoni infection showed histopathological disorders in the splenic architecture of the infected untreated mice[35]. In an almost similar manner, there were severe changes (+++) in the splenic architecture in the infected-untreated animals including dilatations in the blood vessels and splenic foci.

No vasodilatation was noticed in the infected treated groups. Infected groups treated with PZQ or AL showed mild splenic foci. The rats received a high dose of A. sativum (300 mg/kg) extract itself showed deformations in cells of the spleen (white pulp, red pulp, and trabecular) and also the outer capsule[36]. Comparing garlic results in the previous study with Al in the present research, it is showed that that AL, in the opposite way to garlic, did not affect splenic architecture and attenuated the histopathological disorders. In this study, foci were not observed in the infected mice treated with CU. In similar manner, it was reported previously that CU protect the spleens of tumor-bearing mice from pathological disorders[37].

Concerning the kidney structure of the uninfected group, there were hemorrhageic areas in kidneys of animals treated with PZQ, AL, and CU. This hemorrhagic change may be due to the element itself as some drugs caused a hemorrhage in the kidney as investigated by previous authors[38,39].

In the infected-untreated mice, there were malformations in some tubules with severe hemorrhage (++). Some glomeruli were smaller (++), this observation agreed with what reported previously[9]. In all treated groups, there was an improvement in the histopathological architecture in comparison with the infected untreated one. The amelioration in Al and CU groups is due to the ability of these elements in decreasing oxidative stress and hypertension which in turn, affecting the kidney structure[40,41].

CONCLUSION

This study indicated that the bioactive materials (AL and CU) were efficient in the attenuation of histopathological disorders resulting from S. mansoni infection. There was remarkable competitive amelioration of the histopathological changes in liver and spleen sections in groups treated with PZQ or AL or CU. The present research also gave a spotlight on the effect of these elements on the kidney structure.

Hence, we recommend further investigations to use AL and CU as complementary elements with PZQ and more studies on the therapeutic effects of these drugs on liver, spleen, and kidney functions were recommended.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

تأثير البرازيكونتال والألسين والكركمين علي أنسجة الكبد والطحال والكلي في الفئران المصابة بشيستوسوما مانسوني

علي حسين أبوالمعاطي[١]، هدير عبدالحق راشد[١]، مها فريد محمد سليمان[٢]، نهلة سليمان الشناوي[٢]

[١]قسم علم الحيوان- كلية العلوم- جامعة بورسعيد- بورسعيد- مصر.

[٢]قسم علم الحيوان- كلية العلوم- جامعة قناة السويس- الإسماعيلية - مصر.

الخلفية: تعتبر البلهارسيا في الإنسان من الأمراض المتوطنة والتي من الممكن أن تتسبب في تشوهات نسيجية في الأعضاء المختلفة.

الهدف من العمل: تقييم الكفاءة العلاجية المحتملة للبرازيكونتال والألسين والكركمين ضد الأضرار النسيجية الناتجة عن الإصابة بطفيل شيستوسوما مانسوني.

مواد وطرق البحث: تم تقسيم تسعين فأر علي مجموعتين أساسيتين مجموعات غير مصابة ومجموعات مصابة. بداية من الأسبوع السابع للإصابة ، بدأت كل المجموعات في تلقي العلاجات المختلفة. مجموعات البرازيكونتال (٣٠٠ مجم/كجم) عولجت عن طريق الفم لمدة يومين متتابعين. فئران مجموعتي الألسين (٤٠ مللي/كجم) والكركمين (٤٠ مجم/كجم) قد تلقت العلاج عن طريق الحقن داخل الغشاء البروتوني لمدة أسبوعين. ثم تم تسجيل التغيرات النسيجية للكبد والطحال والكلي لتحديد تأثير كل مادة.

النتائج: أستطاع الألسين والكركمين معالجة التغيرات الناتجة عن الاصابة بطريقة تنافسية لنتائج البرازيكونتال. وكان أعلي معدل اختزالي في عدد التجمع الحبيبي في الكبد قد سجل في المجموعة المصابة المعالجة بالكركمين بينما أعلي معدل اختزال في قطر التجمع الحبيبي قد سجل في المجموعة المصابة و المعالجة بالبارازيكونتال. المجموعات المصابة والمعالجة بالبارازيكونتال أو الألسين أحدثت تغيرات طفيفة في تركيب أنسجة الطحال. أفضل نتيجة قد لوحظت في المجموعة المصابة المعالجة بالكركمين حيث لم تسجل أي أضرار في أنسجة الطحال. جميع العلاجات المستخدمة قد أظهرت تغيرات طفيفة في التركيب النسيجي للكلية في الحيوانات الغير مصابة والمصابة.

الخلاصة: هذا البحث يشير إلي الكفاءة العلاجية للألسين والكركمين في علاج التأثير المدمر للشيستوسوما بطريقة تنافسية للبرازيكونتال. علاوة علي ذلك نوصي بمزيد من الدراسات لإستخدام الألسين والكركمين كعلاج مكمل مع البرازيكونتال ودراسة تأثير هذه العلاجات علي وظائف الأعضاء المختلفة.