Assessment of Histopathological Changes in Liver and Spleen of Mice with *Salmonella* Infection Following Combination of Silver Nanoparticles with Amoxicillin Therapy

Original Article

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ABSTRACT

Introduction: Antibiotic resistant *Salmonella typhimurium* and S. *typhi* are a critical health risk in both human and animal medicine. Increasing multidrug resistant strains of *Salmonella spp*. and limited effect of antibiotic led to combined nanomaterial with antibiotic to combat multidrug resistant of pathogenic bacteria.

Aim of the Work: The aim of this study was to evaluate the antibacterial effects of a combined therapy of AgNPs and Amoxicillin against S. *typhimurium* and S. *typhi*, and study impact them of histopathological change in liver and spleen of mice.

Material and Method: S. *typhi* were isolated from patients suffering typhoid fever (systemic infection), and S. *typhimurium* were isolated from patients suffering gastroenteritis including diarrhea. Biosynthesis of AgNPs through reduction of silver nitrate with supernatant of klebsiella pneumonia and reducing agent (glucose). The Amoxicillin and AgNps were prepared according to CLCSI to calculated MIC in the chequerbord method and determined FIC Index. The mice were gavaged with 0.2 ml of *Salmonella spp*. Suspension according to LD50 dose and the control group was gavaged with0.2 ml sterile normal saline. Once a day total daily dose of 100 mg/kg of body weight. After 7 days treatment, assessment of AgNP combined with Amoxicillin in liver and spleen of mice by histopathological study.

Result: All *Salmonella spp* isolates are diagnostic by viteck2 compact system techniques. The LD50 are 3×10^8 and1 $x10^7$ cfu/ml for S. *typhi* and S. *typhimurium* , receptively. The FIC index values for AgNps, amoxicillin combination were 0.5 and 0.7 for S. *typhimurium* and S. *typhi*, receptively. The present study of results histopathological of liver treatment AgNps mixed with Amoxicillin in mice infected with S. *typhi* were binucleated hepatocyte with congested blood vessel and megakaryocyte hyperplasia in spleen. Histopathological spleen treatment of mice by AgNps mixed with Amoxicillin that infected with S. *typhimuriu*m were showed white pulp atrophy, while Histopathological changes in the liver are hydropic degeneration with mild kupffer cell proliferation.

Conclusion: The study showed High doses exposure of AgNps combined with Amoxicillin on mice for testing may cause a mild to moderate toxicity.

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Key Words: Combination AgNps with Amoxicillin, histopathology, liver, *salmonella*, spleen.

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INTRODUCTION

Salmonella enterica represents a major human and animal pathogen *Salmonella* enterica cause systemic and gastroenteritis infections Multidrug-resistant S. enterica serovar *Typhi* (*S. Typhi*) and *S. typhimurium* are increases with biofilm formation[1]. Failure of antibiotics to combat infections caused by multidrug-resistant (MDR) pathogens, especially biofilm formation. Therefore the silver nanoparticles (AgNPs) have been reconsidered as a potential alternative to conventional antimicrobial agents[2]. Highly reactive AgNps exhibit excellent biocidal action against Grampositive and Gram-negative bacteria[3]. AgNPs cause damage to the bacterial cell wall, change membrane permeability of bacteria, moreover, AgNPs interact with DNA, inactivate enzymes, influence metabolic processes, change protein expression and damage the respiratory chain[4]. The β-lactam antibiotics with AgNPs may inhibit hydrolytic β-lactamases produced by bacteria will lead to cell death[5]. The combination of antibiotics with AgNPs seems to be a more effective method for enhancing antibiotic efficacy. The combination attends reduced antibiotic dose requirements, reduced development of bacterial resistance and increased efficiency of co-administered antibiotics[6]. The silver nanoparticles affects spleens were reported in histopathological changes[7]. Silver nanoparticle accumulates mainly in the liver because it contains high

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level of thiol rich proteins such as glutathione . The high and repeated exposure to AgNPs can cause oxidative stress, apoptosis and decreased cell viability in fibroblasts ,hepatocellular degeneration, necrosis[8].

MATERIALS AND METHODS

Samples

S. *typhimurium* were isolated from patients suffering gastroenteritis including (diarrhea), stool samples culture was performed. *S. typhi* were isolated from patients suffering typhoid fever (systemic infection) blood,stool, and urine culture was performed. All samples were cultured according to[9]. The result confirmation by viteck2 compat system techniques.

Synthesis of silver nanoparticles

Silver nanoparticles synthesize at different concentration[10] mM (milliMolary) according to[10,11]. The characterization of silver nanoparticles were achieved in experimental mice. The combinations were assessed according to[12,13].

Estimation of Lethal Dose 50 (LD50)

84 mice albino with average weight of the study group was 25.0±4.3 grams and 6- 8 week-old female mice were obtained from animal house of Al Yarmouk center for cancer and genetic researches in Baghdad which were used in basic research. Mice were transferred to the animal house of college science in Anbar University and adapted for one week before experiments started. 42 mice infected with S. *typhimurium* and 42 mice infected with *S. typhi* were used to estimate LD50(divided to six groups) according to[14]. All groups infected were observed for 30 days to calculate the live and dead mice and determine lethal dose according to[14].

Animals grouping

42 of mice with average weight of the study group was 25.0±4.3 grams and 6- 8 week-old female mice with 25-30 c0 and (35- 60) of humidity . 21 mice infected with *S. typhimuium* and 21 mice infected with *S. typhi*. Three groups of them were divided in this study and each group consist of 7 mice , that included : The first group that used as a control was administered by 0.20 ml normal saline only (control negative). The second group was infected orally with 0.2 ml *S. typhimurium* according to LD50 without treatment (control positive) .The third group was infected orally with 0.2 ml (LD50) of *S. typhi* and after 3nd day post infection was treated with 0.2 AgNps combined with Amoxicillin with concentration 100 mg/kg/day according to MIC concentration by chequer board method. The same protocol were used with *S. typhi*.

Bacterial strains and growth conditions

Bacteria was isolated according to[9]. The mice should be soured, that all animals were pathogen free by bacteriological examination showed that the mice were negative culture for bacterial pathogens at the beginning of the study,then was deprived of food overnight and of water for 3 hours. The mice were housed in cages and fed with sterilized water and food The *Salmonella* enterica were recovered from the intestine of mice. The mice were sacrificed and their small intestinal were extracted, homogenized in sterile phosphate buffer solution (PBS) and bacteriological procedure according to[15].

Mechanism of anti-bacterial administration dose

The mice infected with *S. typhimurium* and *S. typhi* and after three days(post infection. once a day total daily dose of 100 mg/kg of body weight according to[16] and then results were shown symptom and sign of animals[17].

Antibacterial solution preparation

The solutions of Amoxicillin and AgNps were prepared according to minimum inhibitory concentration in the chequerbord method. Amoxicillin (Bioanalyse, Turkey) and AgNps was synthesis by biological method. According to Özkaya *et al*.[15] one mouse in each group were sacrificed after 3th days post infection and compare their results of each group by sacrificed and blood taken (from their heart and some intestines) from mice were cultured on,Macconcky agar for 24 hours at 37 c0. By Vitek2 compact system techniques to confirm presence of Salmonell Spp.

All mice in each group were sacrificed after 7th day (post treatment)[17]. The study results histopathology between liver and spleen of all groups, and study how to effected of this bacteria and combination AgNps with Amoxicillin (toxicity) to the tissue of this organs.

Histopathological examination

Tissue specimens from liver, and spleen were collected for histopathological examination under light microscope followed the standard protocol. Tissue sections of 3-5µm thick were cut, stained with Haematoxylineosin (H&E). The results were recorded using a digital camera system attached to microscope for histopathological examination[18]

RESULT

The present study was showed AgNP synthesize under optimal conditions as a function of time, supernatant of Klebsiella pneumonia, 10 mM solution glucose and PH= 9.0 - 9.5 were changed in color from light yellow to brown during synthesis of AgNPs according to[10,11]. The synthesis and characterization of silver nanoparticles were shown in data supplement. The combination impact of Amoxicillin with AgNPs against S. typhimurium and S. typhi isolates were estimated by chequerboard method. The FIC index values for AgNps, Amoxicillin combination were additive (0.5 and 0.7) for S. typhimurium and S. typhi, receptively. The combination of AgNps and Amoxillin were observed.

control groups

In the present study ,.the control group's mice specimens showed a normal architectures of spleen of (control) and

liver not showed any changes with normal blood vessels and normal hepatocyte in (Figures 1,2).

In the histopathological study of the spleen treatment of mice by combination of AgNps and Amoxicillin that infected with S. typhimurium were showed white pulp atrophy in (Figure 3).

The histophotographic study of mice liver treated by AgNps combination with Amoxicillin that infected with S. typhimurium were showed hydropic degeneration with mild kupffer cell proliferation in (Figure 4).

The histological finding of mice spleen which was treated with AgNps amoxicillin against S. typhi showed megakaryocyte hyperplasia in (Figure 5).

The histopathological liver treatment of AgNps mixed with amoxicillin in mice against S. typhi was showed binucleated hepatocyte with congested blood vessel in (Figure 6).

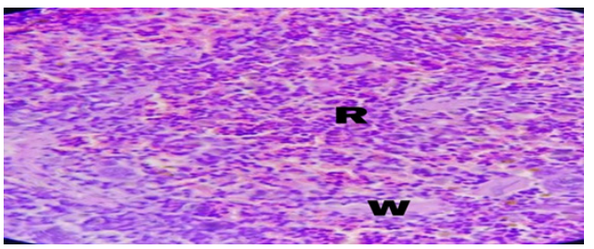

Fig. 1: The spleen section of mice control group exhibited normal white(W) and red pulp(R). Stained with H&E, (40 x).

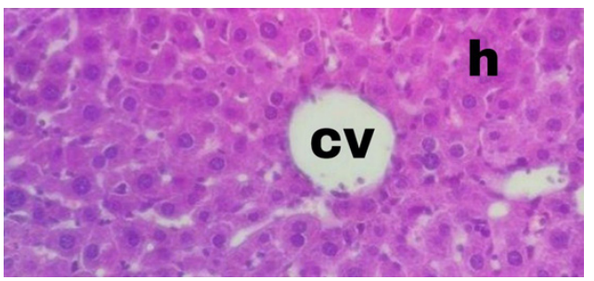

Fig. 2: The liver section of control group exhibited normal architectures includes normal (central vein) (cv) and normal hepatocyte(h).stained with H &E, (40x).

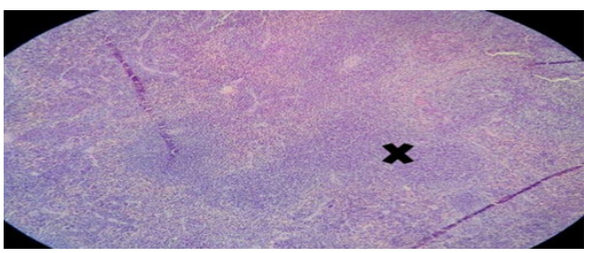

Fig. 3: The section of spleen of (The AgNps mixed with Amoxicillin treatment of spleen in mice against S. typhimurium). showed white pulp atrophy (X). H &E stain 10x).

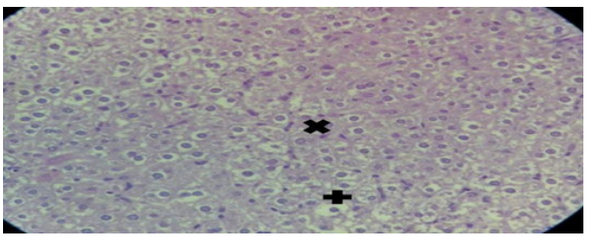

Fig. 4: The section of liver of (The AgNps mixed with Amoxicillin treatment of liver mice against S. typhimurium) group . showed hydropic degeneration (+) with mild kupffer cell proliferation(X). H &E stain X40).

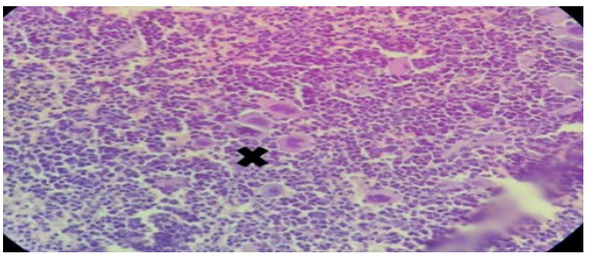

Fig. 5: The section of spleen of (AgNps mixed with Amoxicillin treatment spleen of mice from S. typhi) .showed megakaryocyte proliferation(X). (H &E stain X40).

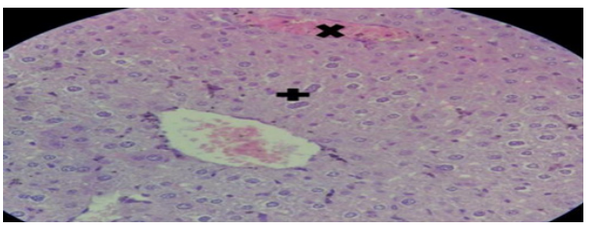

Fig. 6: The section of liver of (The AgNps mixed with Amoxicillin treatment liver of mice in S. typhi) group .showed binucleated hepatocyte (+) with congested blood vessel(X). (H &E stain X40).

DISCUSSION

These additive activities of AgNps in the presence of Amoxicillin were effected against Salmonella strains, it might be possible to reduce the viability of bacterial pathogen at lower antibiotic concentrations[19].

The control negative control as mean without infected with S. typhimuriun and S typhi. Santosh *et al*.,2010 Reem *et al*.,2019[20] are agreed with present study of the normal blood vessels and normal hepatocyte of mice in (Figures 1,2).

The morphological changes of spleen when treatment of mice by combination of AgNps and Amoxicillin that infected with S. typhimurium in (Figure 3) were showed white pulp atrophy when compared to the control group. Silver nanoparticles caused spleen color changes and atrophy in mice groups. Hassanen *et al*.,2019 reported ,that spleen damages, due to increased doses in experimental animals or *Salmonella* invasive[21].

Histological assessment of the liver after treatment with AgNps showed the presence of moderate lesions exhibiting leukocyte infiltration, hydropic degeneration and/or necrosis as (figure 4). Kosif *et al*.,2010 reported the hydropic degeneration Kupffer cell proliferation, compared with control, that refers to the occurrence of reversible intracellular edema as a consequence of toxic, infectious or immune aggressions. The increase in cell volume and clearness was associated with the formation of microvacuoles or clear cytoplasmic spaces as a result of the action of injurious agents and increase in water content[22].

In this study the results showed after therapy with AgNPs, the histological liver changes after one week shows an aggregation of lymphocytes, hydropic degeneration and active proliferative of kupffer cells and necrosis. the hepatotoxicity of activity AgNps in murine model of salmonella infection, after 7 day of treatment included an increase swollen, and vacuolization, of hepatocyte, that could be attributed to alteration in water homeostasis that may be caused by free radical, during reduction[23]. These results are in agreement with[24].

When mice was treated with AgNps amoxicillin against S. typhi ,the spleen of mice showed megakaryocyte hyperplasia in (Figure 5). The megakaryocyte proliferation, may attribute to the spleen bleeding or any other area ,due to salmonella infection and a variety of conditions, such as hematotoxic insult, systemic anemia, infection, hemorrhage, and neoplasia[25]. The excessive hematopoiesis in the mouse spleen was generally recognized as a reactive process. The mouse spleen has extensive potential for reactive hematopoiesis in response to inflammatory, neoplastic, or hematopoietic insults, and this has been described as being so extensive as to mimic neoplasia[26]. The spleen may enlarged with increased hematopoiesis that may involve erythropoiesis, myelopoiesis, and/or megakaryocyte hyperplasia with histologic features of splenic cavity filled with hemopoietic elements and atrophic white pulp[27]. Ward *et al*.,2012[28] Similarly result with the present study.

The binucleated hepatocyte with congested blood vessel showed when treatment of AgNps mixed with amoxicillin in mice against S. typhi as (Figure 6).

The binucleation cells, due to the nuclear division not followed by cytoplasmic division. Binucleation results from cytokinesis failure that takes place progressively during the course of postnatal development. The proportion of binucleation was increased with the aging process or with cellular stress such as surgical resection, toxic stimulation, metabolic overload, or oxidative damage, to involve as much as 90% of the hepatocytes in mice[29]. Gentric *et al*.,2015[30] reported the hepatic binuleated could be modified by metabolic overload, DNA damage, and chemical induced liver injury, like overloads of copper and iron in the liver. Hepatocytes had increased binuleated with delayed mitotic progression ,furthermore, binucleated was increased following exposure to radiation or oxidative stress[30]. Also Anatskaya *et al*.,2010[31] mentioned the binucleated hepatocytes was served to enhance hepatocyte function. The liver participates in a wide array of activities related to protein synthesis/secretion, metabolism, and detoxification. The diploid hepatocytes were indicated induces genes fighting against pathogens, DNA lesions, oxidative stress and inhibits genes promoting apoptosis. Nadia *et al*.,2018[32] similirity results with present study.

The oral dose administrated to mice of AgNPs at 100mg/kg concentrations lead to congestion of blood vessels of liver., and increases of (distention) blood capillaries in mice that more blood cells are reaching the liver faster, a process described as ‘‘vessel congestion.’’ According to Booth and Mcdonald[33], this process facilitates white-cell migration; neutrophils, monocytes, and lymphocytes, and, among other cells, participates in the inflammatory process and/or the removal of foreign substances[34]. These result are in agreement with[35].

CONCLUSION AND SUMMARY

The study shows that AgNPs have potential as adjuvants for the treatment of mice bacterial diseases. the anti-bacterial agent of S. enterica serovar *Typhimurium* and S. enterica serovar Typhi at sub-MIC level were inhibited bacterial growth and promotes changes in morphology of the cell. The results of histological study against mice when treated with combination between AgNps and Amoxicillin showed the antibacterial were succeeded to kill S. enterica serovar Typhi and S. enterica serovar *Typhimurium* but affected to liver and spleen of mice infected compared with control negative.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

التحري عن التغيرات النسيجية المرضية في الكبد والطحال للفئران المصابة ببكتريا السالمونيلا والمعالجة بمزيج من جزيئات الفضة النانوية وعقار الاموكسيسلين

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مقدمة: مقاومة المضادات الحيوية Salmonella typhimurium and S. typhi تشكل مخاطر صحية خطيرة على كل من الوضع الصحي للإنسان والحيوان. ان زيادة سلالات السالمونيلا المقاومة المتعددة للأدوية. أدى التأثير المحدود للمضادات الحيوية الى التحري عن تآزر المواد النانوية مع المضادات الحيوية لمكافحة البكتريا المسببة للامراض والمقاومة للعديد من المضادات للحيوية .

هدف العمل: كان الهدف من هذه الدراسة هو تقييم التأثير التآزري للمضاد الاموكسيسلين مع جزيئات الفضة النانوية ضد بكتريا S. typhimurium و S. typhi ، ودراسة تأثيرهما على التغيير النسيجي المرضي في الكبد والطحال للفئران .

طرق العمل: تم عزل S. typhi من مرضى يعانون من العدوى الجهازية بحمى التيفود و S. typhimuriumتم عزلها من مرضى يعانون من التهاب المعدة والأمعاء بما في ذلك الإسهال. التخليق الحيوي للـ AgNPsتم من خلال اختزال نترات الفضة مع عالق بكتريا Klebsiella pneumoniae باضافة عامل الاختزال الجلوكوز. تم تحضير أموكسيسلين و AgNpsوفقًا لـ CLCSI لحساب MIC حسب طريقة جكربورد ومؤشر FIC المحدد.

تم تطعيم الفئران بـ ٠,٢ مل من معلق Salmonella spp. حسب جرعة LD٥٠ ومجموعة المراقبة تم تعقيمه بـ ٠,٢ مل من محلول ملحي معقم. تم اعطاء جرعة يومية إجمالية قدرها ١٠٠ مجم / كجم من وزن الجسم مرة واحدة في اليوم من محلول الاموكسيسلين مع جزيئات الفضة النانوية. بعد ٧ أيام من العلاج ، تم تقييم اثر التطعيم في الكبد والطحال للفئران من خلال دراسة الأنسجة المرضية.

النتائج: تم تشخيص جميع عزلات Salmonella spp بنظام viteck٢compact . إن LD٥٠ هي ٣ × ١٠٨ و ١ × ١٠٧CFU / مل لكل من S. typhi و S. typhimurium ، على التوالي. كانت قيم مؤشر FIC لتركيبة AgNps ، أموكسيسلين ٠,٥ و ٠,٧بالنسبة لجرثومة S. typhimurium و S. typhi ، على التوالي. اظهرت نتائج الدراسة النسيجية المرضية للكبد المجرع ب AgNpsمع أموكسيسلين في الفئران المصابة ب S.typhi.تضخم في الطحال واحتقان الاوعية الدموية مع ظهور خلايا ثنائية النوى . في حين اظهرت مقاطع الطحال للدراسة النسيجية المرضية للفئان المجرعة بجزيئات الفضة النانوية المرتبطة بالاموكسيسلين والمجرعة بـ S. typhimurium.ظهور ضمور اللب الأبيض ، في حين أن التغيرات النسيجية المرضية في الكبد هي انحلال مائي مع تكاثر خفيف في خلايا كوبفر .

الاستنتاج: أظهرت الدراسة أن التعرض لجرعات عالية من جزيئات الفضة النانوية مع أموكسيسلين في فئران الاختبار قد يسبب سمية خفيفة إلى معتدلة.