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Original Article

Study of Antimicrobial Activity of Silver Nanoparticles against *Salmonella Typhi* Infections *in Vitro*

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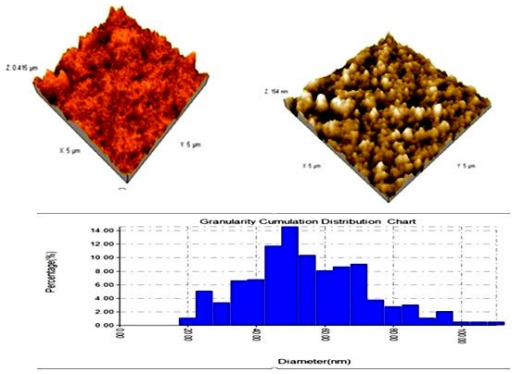
ABSTRACT

The aim of this study is to investigate the antibacterial effect of silver nanoparticles (AgNPs) against multidrug-resistant *Salmonella typhi* recovered from blood, stool, and fluid specimens. *In vitro* the antimicrobial activity of silver nanoparticles against *S.typhi* isolates done by determination of silver nanoparticles activity by agar wells diffusion assay, MIC, sub MIC, and by Microtiter plate (Submic). By agar wells diffusion assay and MIC**,** the antimicrobial activity of silver nanoparticles showed an inhibition zone, among 50 strains of *S.typhi*. Five Submic showed that sensitivity was higher among Submic 1, 2, and 3 than those in Submic 4 and 5 that show higher resistance (96%, 94%, and 86% vs. 4%), respectively. By Microtiter plate when we used three diluted concentrations of silver nanoparticles of Submic 1, 2, and 3, significant were found that after 24 hours was significantly higher than that after 48 hours, as Submic 1 (0.19874 ± 0.034156 vs. 0.14864 ±0.025908), respectively with mean differences of 0.050100 (t= 9.794, df: 49, P=0.000) and the means of Submic 2 and 3 was (0.20776 ± 0.031197 vs. 0.15730 ± 0.027060) (t=10.401, df: 49, P= 0.000) and (0.21464 ± 0.030793 vs. 0.16802 ± 0.026111) with mean differences of 0.050460 and 0.046620, respectively and (t= 9.031, df: 49, P= 0.000, respectively. Antibacterial activity of silver nanoparticles has been demonstrated in several investigations, but the reported MIC values range through a wide extent of variation. In our study, silver nanoparticles showed a good antibacterial activity against all the tested pathogens. The results of MIC and Submic tests revealed a higher MIC value for *S.typhi* compared with the other tested pathogens. It is possible that AgNPs act similarly to the antimicrobial agents used for the treatment of MDR *S.typhi* infections, which show four different mechanisms of action including: interference with cell wall synthesis, inhibition of protein synthesis, interference with nucleic acid synthesis, and inhibition of the metabolic pathway.

GRAPHICAL ABSTRACT



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Introduction

One of the most widely spread diseases typhoid fever, which is relatively linked to proper sanitation, and is probably responsible for among (2-5%) of mortality, the causative agent of this disease is *Salmonella typhi*.

Salmonella typhi is a Gram-negative rod, flagellated, encapsulated, non-spore-forming, and facultative anaerobic [1].

Antimicrobial usage for therapy is the mainstay of typhoid treatment, successfully employed "Chloramphenicol" to cure typhoid fever. The emerging multiple drug resistance (MDR) among the bacterial strains is on the rise, and becoming increasingly widespread, and also includes the resistance of older antimicrobials such as "Chloramphenicol", "Ampicillin", and "Trimethoprim-Sulfamethoxazole" (Co-Trimoxazole) has been existed for many years and this issue is considered as the first problem in holding typhoid fever. As a result, "Fluoroquinolone", as "Ciprofloxacin", has been chosen as the first-line antibiotic for therapy, particularly after the widespread rise of multidrug-resistant *S. typhi* isolates [2]. The transition to ciprofloxacin has resulted in a rise in the number of typhoidal *Salmonellae* resistant to the antimicrobial drug [3].

Nanoparticles of silver are smooth, gloss, and white transition metals with excellent electrical and thermal conductivity, it known for a long time of recorded history due to its medicinal and therapeutic properties, prior to discover that bacteria were infection agents. It is employed in different methods like coins, cups, dishes, solutions, foils, sutures and colloids like lotions and ointments. In medicine, the most effective treatment for infectious disorders and surgical infections was silver, which has more advantages than disadvantages [4].

When silver is introduced into bacterial cells, it causes a lot of structural and morphological changes, which can lead to the cell death by cling to the cell wall and cell membrane when they come into touch with bacteria part of the silver travels through to the interior, where it interacts with phosphate-containing molecules such as DNA and RNA, while the rest attaches to the membrane's sulfur-containing proteins. They generate structural changes in the cell wall, such as the creation of pits and pores [5].

Materials and methods

Specimen's collection

A total of 200 clinical samples of blood, stool, and fluid were collected from patients with pyrexia of unknown origin and gastroenteritis from teaching laboratories and other laboratories of the medical city of Baghdad, Iraq, and private labs during the period November 2021 to March 2022. These specimens were 120 blood, 60 stool, and 20 Ascitic fluid.

Ten milliliters (10 mL) of venous blood or Ascitic fluid were obtained from each patient and added to 50 ml of brain heart infusion bottles were loaded into BacT/Alert instruments, the bottles remain in 5 days BacT/Alert, loopful took in sign positive subculture on blood agar and MacConkey agar by streaking method then incubation 36°C ±1 for 24 hours**.** The stool was cultured on xylose lysine deoxycholate and MacConkey agar by streaking method, incubated at 36 °C±1 for 24 hours [6].

Identification of S.typhi

The identification of the organisms was performed by the tests as described by [7] on the basis of the colony.

Biochemical tests: Oxidase, catalase, Kligler Iron Agar (KIA), indole production, citrate utilization, and urease production were performed and described as by (Brooks *et al.*, 2007) [7].

Analytical profile index (API20E) were performed and described as by (Beshiru *et al.*, 2019) [8].

3. Vitek-2 System were performed and described as by (Pathak, 2021) [9] and (Moin, 2020) [10].

Serological test

A confirmatory test was done in a central public health laboratory by using polyvalent antisera and monovalent antisera for *S.typhi*.

Antimicrobial susceptibility testing

According to the clinical laboratory standers institute, this test was performed by the method of Kirby-Bauer (1968) (disk diffusion) technique using Muller-Hinton agar and different single antibiotic disc supplied commercially. Antibiotic susceptibility and resistance were determined by strain growth zone diameter [11].

Biosynthesis of bacteriocins with silver nanoparticles (Bac-SNPs)

The Bac-SNP suspension was made with silver nitrate ($AgNO_3$), 2 mg silver nitrate in a 20 mL aliquot of purified bacteriocins ultra- sonication for 10 minutes to disseminate the mixture. The SNPs production was indicated by a change in hue from light yellow to reddish-brown. The obtained suspension was shaken for 24 hours at 120 RPM, and then centrifuged at 10,000 rpm for 20 minutes, removing the filtrate and washing the sediment twice with Deionized distal water (D.D.W), and then it was centrifuged at 10,000 rpm for 10 minutes. Thereafter, the sediment was placed in a petri dish and placed in an incubator for 24 hours [12].

Characterization of silver nanoparticles

The characterizations of the addressed materials were investigated by using several analysis techniques such as field emission scanning electron microscopy (FE-SEM), Fourier transforms infrared spectroscopy (FT-IR), X-ray diffraction (XRD), ultra-violate visible light spectroscopy (UV-Vis), and atomic force microscopy (AFM). The above-mentioned techniques are described in detail in the following subsections:

The UV-Vis spectra analysis were performed and described as by (Fazal-ur-Rehman *et al.*, 2020) [13].

The atomic force microscopy (AFM) analysis, Fourier transform infrared spectroscopy (FTIR), and X-Ray Diffraction (XRD) were performed and described as by (Pola *et al.*, 2020) [12].

Determination of silver nanoparticles concentration

An advanced microwave digestion system was used for digestion of the AgNPs sample, and the Ag+ concentration was determined by using elemental concentrations of the nanoparticle solution. Atomic Absorption Spectrometer (AAS) in which argon gas was used for excitation of the element atom and the blank value for the element was deduced from the sample value.

Antibacterial activity by using AgNPs

In vitro antibacterial activity is done by the following:

Determination of Silver nanoparticles activity by agar wells diffusion assay (MIC) [14].

Antibacterial activity was determined against *Salmonella typhi* and the stock solution adds 0.1 mg of AgNPs in 10 mL D.D.W.

Nine serial dilutions of silver nanoparticles were prepared (µg/mL) by using D.D.W, (1.2, 1. 4, 1.8, …, 1.512) and after any dilution, the ultra-sonication was used.

A sterile well borer was used to hole 3-4 wells of 5 mm diameter wells in each late after an aliquot of 100 µl of each culture was placed uniformly on fresh Muller Hinton plates. 50 µl of the test solution was incubated in an upright position at 36±1 °C for 24 hours in each plate. A scale was used to record the zone of inhibition obtained.

Determination of Silver nanoparticles activity by agar wells diffusion assay (Sub MIC)

Five serial dilutions of silver nanoparticles were prepared in tube of dilution number 5 (µg/mL) by using D.D.W that Sub Mic (1.2, 1.4, 1.8, 1.16, and 1.32) and after any dilution ultra-sonication was used.

An agar well diffusion assay was used to test the antibacterial activity of AgNPs. Strains were cultured overnight in MacConkey agar against *Salmonella typhi*, and an antibacterial analysis was performed on freshly developed cultures. A sterile well borer was used to hole 3-4 wells, 5 mm diameter wells in each plate after an aliquot of 100 µl of each culture was placed uniformly on fresh Muller Hinton plates. 50 µl of the test solution was incubated in an upright position at

36±1 °C for 24 hours in each plate. A scale was used to record the obtained zone of inhibition.

Determination of silver nanoparticles activity by Microtiter plate (Submic 1.2, 1.4, and 1.8)

By using sterile 96-well polypropylene microtiter plates, the micro broth dilution method was applied.

TSB (tryptic soy broth), and then inoculated with 2-3 colonies of *S. typhi* from overnight cultured on MacConkey, and then it was incubated in 36±1 °C at 24 hours with dilution to 1:100 in new TSB.

The reference strain of *S. typhi* ATCC19430 was used as a positive control, and wells inoculated with the sterile broth was used as a negative control.

100 µl volume was moved in two microtiter plates and 100 µl (50 µl TSB+ 50 µl Sub mic in 3 dilutions of SNP) was added. One plate was incubated in 36±1 °C for 24 hours and read of OD by Elisa reader that showed the *S.typhi* inhibition.

Plate two was incubated for 48 hours. 100 µl (50 µl TSB+ 50 µl Sub mic in 3 dilutions of SNP) was added and OD was read in Elisa reader that showed inhibition of the mentioned *S.typhi* biofilm.

Results and Discussion

The body samples of the total patients were collected and cultured after inclusion and exclusion criteria. Out of total cultured samples 50 (25%); *S.typhi* bacteria were isolated from different samples mainly in blood followed by stool and fluid (74%, 24%, and 2%), respectively, as displayed in Figure 1.

The identification of bacteria

Culture identification

On differential medium which is XLD agar the colonies appear red with black centers, while on MacConkey agar, the colonies appear smooth, pale, transparent, colorless, and raised colonies.

Biochemical test

Api 20 E system

API 20 E system was performed to confirm the diagnosis, as depicted in Figure 2 and Table 1.

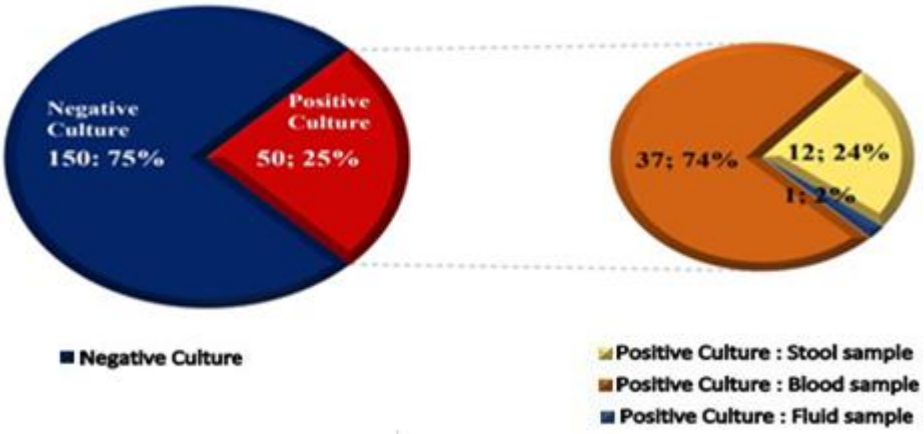

Figure 1: Prevalence *of S. typhi* isolation among sample cultures (n=200)

Table 1: Biochemical test results for *S.typhi*

Biochemical tests	Results
Oxidase	-
Catalase	+
Kligler iron	Acid /Alkaline no gas with H2S
Simmon citrate	-
Urea test	-
Semisolid mannitol	Motile /mannitol fermentation
Peptone water for indol	-

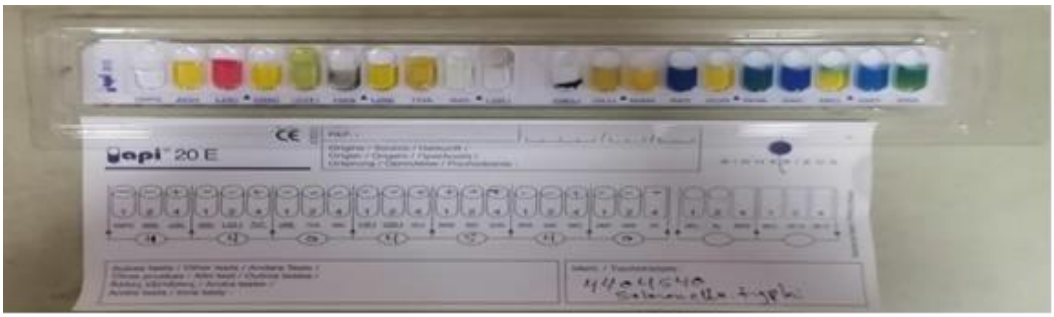

Figure 2: The results of the API 20E test used for the *S.typhi* identification

Serological test

Slide agglutination method by using polyvalent and monovalent antiserum for *Salmonella* somatic and flagellar antigen, the result revealed agglutination for all 50 isolates diagnosed before. This test is easy, fast, and more accurate.

VITEK 2 System

The acquired results from the VITEK 2 test for *S. typhi* are demonstrated. It is worth mentioning that the GN card was used for gram-negative bacteria which are consisted of 47 biochemical examinations and matches 95%.

Characterization of silver nanoparticle

UV-Vis spectroscopy

The corresponding UV-Vis absorption spectra are indicated in Figure 3. The UV–visible spectra of synthesized AgNPs were recorded in the range of 290-4200 nm. The samples exposed to the silver nitrate solution show a wide spectrum range of around 375 nm.

Fourier-transform infrared spectroscopy (FT-IR) analysis

The FT-IR spectrum of biosynthesized silver nanoparticles showed that nanoparticles manifest absorption peaks located at about 1056.99, 1396.46, 1585.49, and 3290.56 cm^{-1} in the region 400-4000 cm^{-1}. The peaks at 3290.56 cm^{-1} were assigned to O-H stretching. The band at 1585.49 cm^{-1} is associated with the C-H stretch of the methylene groups of the protein. The band at 1056.99 and 1396.46 cm^{-1} corresponds to the N-H bond of primary amines due to carbonyl stretch in proteins, as depicted in Figure 4.

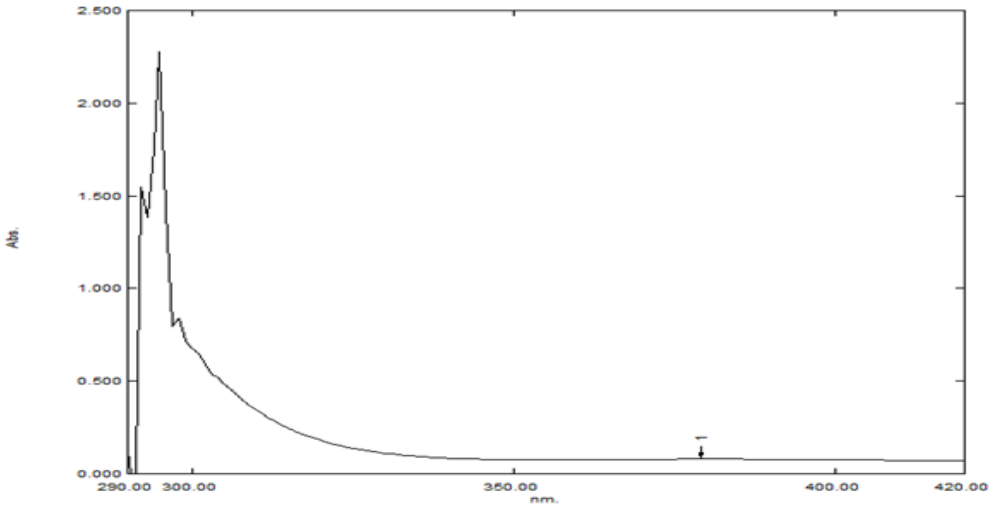

Figure 3: UV-Vis spectrophotometry of silver nanoparticles biosynthesized by *Lactobacillus* bacteriocins

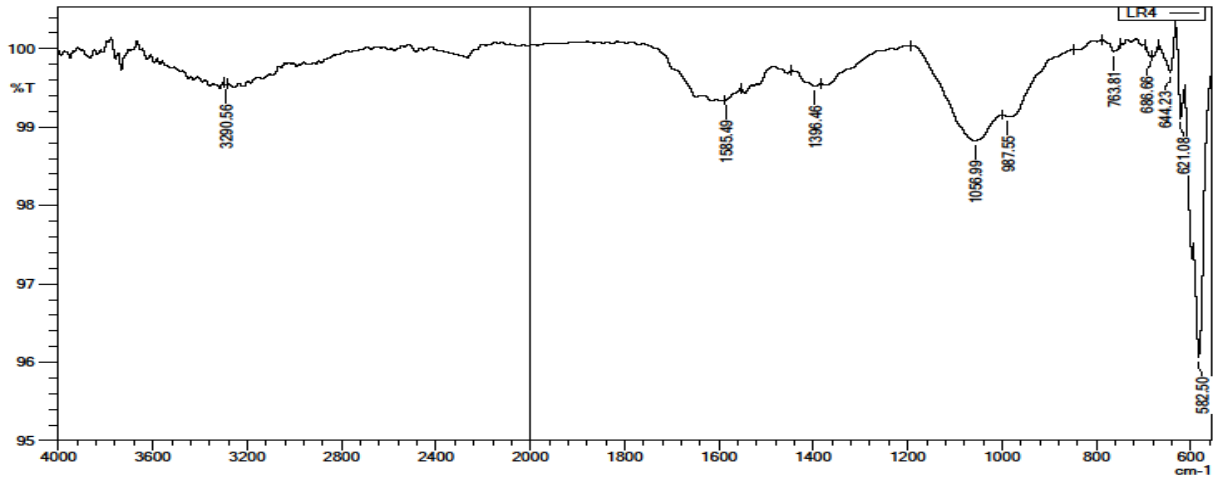

Figure 4: FT-IR analysis of silver nanoparticles biosynthesized of bacteriocins isolate from *lactobacillus*

Atomic force microscope (AFM)

The AFM provides a 2D and 3D view of the surface of nanoparticles at an atomic level. In nanoscale size, the average particle diameter was calculated. The AgNPs made with bio-surfactant were investigated by using AFM. Because of factors that affect results, such as pollution, surface analysis (AFM) necessitates the close attention. AFM-SPM was used to estimate the size of silver nanoparticles, the average size of AgNPs was 52 nm, according to the results indicated in Figure 5.

X-ray diffraction (XRD)

The results revealed in Figure 6 that there are eight-strong different diffraction peaks corresponding to the crystal planes of crystalline AgNPs observed at 2θ (θ=diffraction angle) values of 32.5°, 33.6°, 38.3°, 46.5°, 57.7°, 64.7°, 70.9°, and 77.3. The mentioned peaks are matched with the diffraction data standard of AgNPs (JCPDS file no. 4-783). The values corresponding to the crystalline distance (d) of (2.7), (2.6), (2.4), (2.3), (1.9), (1.6), (1.5), (1.4), (1.3), and (1.2).

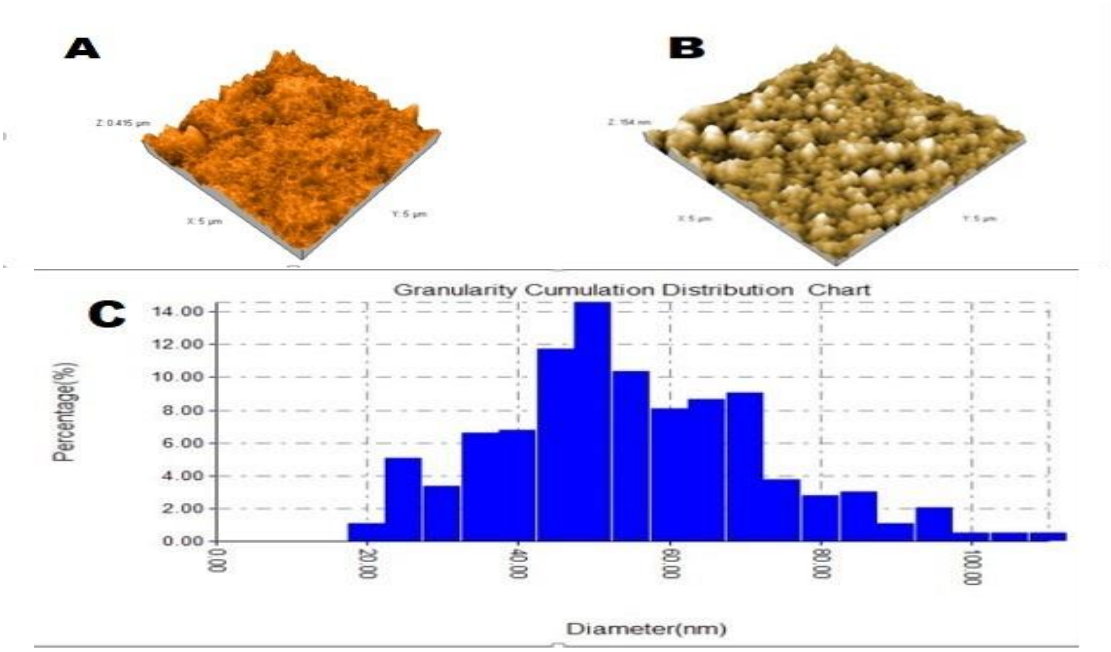

Figure 5: Biosynthesized AgNPs by isolate of *S.typhi* under AFM (A) 2D image of silver nanoparticles synthesis, (B) 3D image of silver nanoparticles synthesis, and (C) granularity distribution chart of silver nanoparticles synthesis

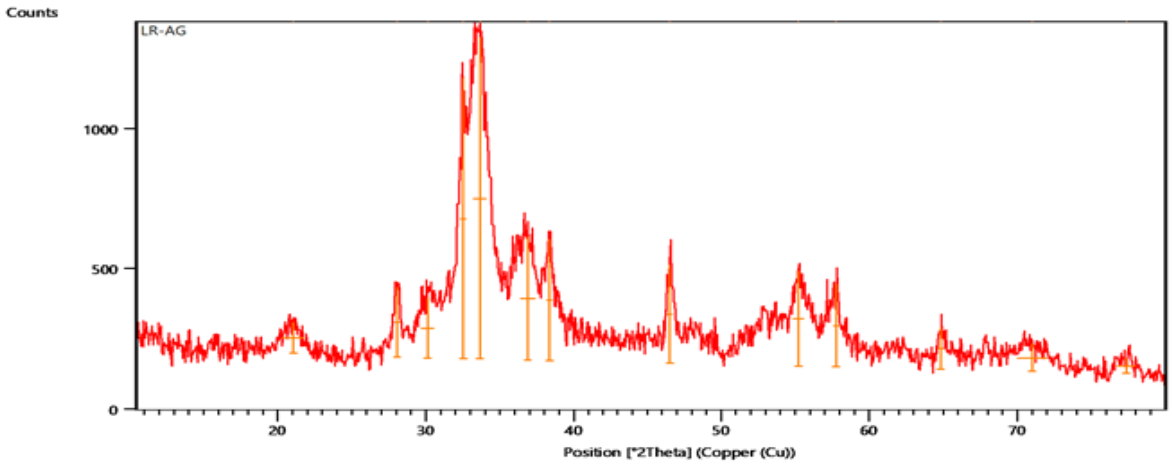

Figure 6: X-ray diffraction (XRD) analysis

Antibiotic susceptibility by disc diffusion method (DDM) and VITEK2 compact system

The result of phenotypic test by using disc diffusion method and VITEK2 compact system is presented in Tables 2 and 3.

Silver nanoparticles biosynthesis

The conical flasks contained the aqueous silver ions which were reduced to silver nanoparticles when added to the aliquot of purified bacteriocins. It is observed that the color of the solution turned from light yellow to reddish-brown after 24 hrs. of the reaction, which indicated the formation of silver nanoparticles extracellularly. The formation and stability of the reduced silver nanoparticles in the colloidal solution was the Ag+ concentration was determined by using elemental concentrations of the nanoparticle solution Atomic Absorption Spectrometer (AAS).

Antibacterial activity by using of AgNPs in vitro antibacterial activity

Determination of silver nanoparticles activity by agar wells diffusion assay and (MIC)

The antimicrobial activity of silver nanoparticles synthesized by bacteriocins of *lactobacillus* was investigated against, *S. typhi*. Regarding the inhibition zone, Table 4 demonstrates the antimicrobial silver nanoparticles concentration and inhibition zone among 50 strains of *S.typhi* shown in Petri Dish, as in strain *Sal.* 48 showed the full resistance of antibiotics.

Table 2: Number and percentage of resistant and sensitive isolates against tested antibiotics

No.	Name of antibiotics	S.typhi isolates resistance (blood)	S.typhi isolation resistance (stool)	S.typhi isolation sensitive (blood)	S.typhi isolation sensitive (stool)	S.typhi isolation sensitive (fluid)
1	Ampicillin	34	13	2	0	1
2	Azithromycin	15	9	22	3	1
3	Ciprofloxacin	32	9	4	4	1
4	Levofloxacin	29	8	7	5	1
5	Ofloxacin	31	9	4	5	1
6	Trimethoprim-sulfamethoxazole	1	1	35	12	1
7	Cefotaxime	35	13	1	0	1
8	Ceftriaxone	34	13	2	0	1
9	Tetracycline	29	14	3	3	1
10	Chloramphenicol	7	12	20	10	1

Table 3: Number and percentage of resistant and sensitive isolates against tested antibiotics by using Disc diffusion test (n= 10) depend on clinical and laboratory standards institute (CLSI)

No.	Name of antibiotics	Code	Disc potency (µg/disc)	Salmonella typhi isolates resistance	Salmonella typhi isolation sensitive
1	Ampicillin	AM	10 µg	47	3
2	Azithromycin	AZM	15µg	24	26
3	Ciprofloxacin	CIP	5 µg	41	11
4	Levofloxacin	LEV	5 µg	37	13
5	Ofloxacin	OFX	5 µg	40	10
6	Trimethoprim – sulfamethoxazole	SX T	25 µg	2	48
7	Cefotaxime	CXT	30 µg	48	2
8	Ceftriaxone	CRO	30 µg	47	3
9	Tetracycline	TE	30 µg	34	7
10	Chloramphenicol	C	30 µg	19	31

Table 4: Concentration and inhibition zone of silver nanoparticles

Dilution of silver	Concentration (ppm)	Inhibition zone
Total sliver	1.368	20
Mic 1(1/2)	684	19
Mic 2 (1/4)	342	18
Mic 3 (1/16)	171	17
Mic 4 (1/32)	85.5	16
Mic 5 (1/64)	42.75	14
Mic 6 (1/128)	21.375	12
Mic 7 (1/256)	10.375	11
Mic 8 (512)	5.34375	9
Mic 9 (1/1024)	2.671875	8

Furthermore, after five dilutions of the Mic 5 (1.64) of 42.75 concentration and 14 diameter inhibition zone, the frequency of five Submic showed that sensitivity was higher among Submic 1, Submic 2, and Submic 3 than those in Submic 4 and Submic 5 that shows higher resistance (96%, 94%, and 86% vs. 4%), respectively, as depicted in Figure 7.

Determination of silver nanoparticles activity by Microtiter plate (Submic 1, 2, and 3)

When using three diluted concentrations of silver nanoparticles of Submic 1, 2, and 3, the significant differences were found, as Submic 1 after 24 hrs. was significantly higher than that after 48 hrs. (0.19874 ± 0.034156 vs. 0.14864 ±0.025908), respectively, with mean differences of 0.050100 (t= 9.794, df: 49, P=0.000) (Figure 8). Similarly, the means of Submic 2 and Submic 3 after 24 hrs. were significantly higher than those after 48 hours (0.20776 ± 0.031197 vs. 0.15730 ± 0.027060) (t=10.401, df: 49, P= 0.000) and (0.21464 ± 0.030793 vs. 0.16802 ± 0.026111) with the mean differences of 0.050460 and 0.046620, respectively, and (t= 9.031, df: 49, P=0.000), respectively (Figures 9 and 10).

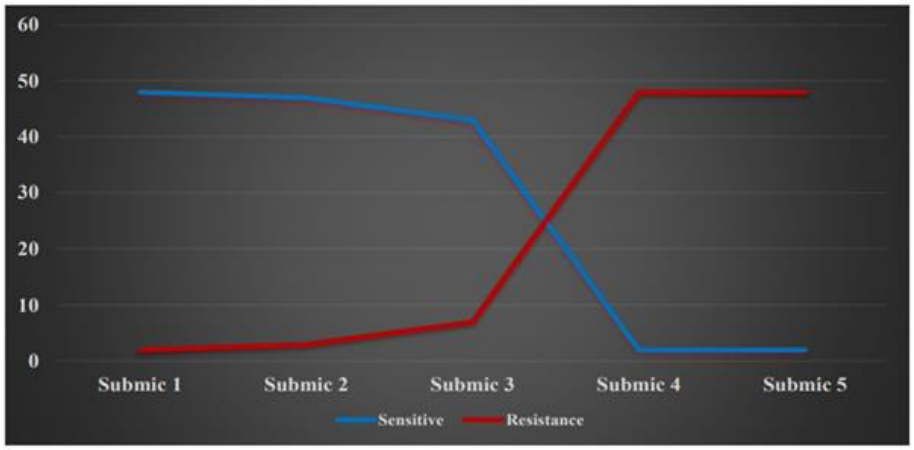

Figure 7: Sensitivity of mic 5 sliver nanoparticles

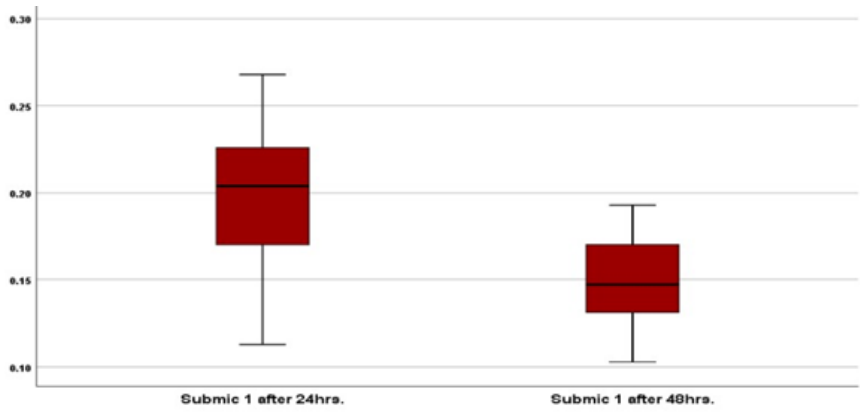

Figure 8: Means comparison of Submic1 silver nanoparticles after 24 and 48 hrs. (n=50); the paired t- test was used

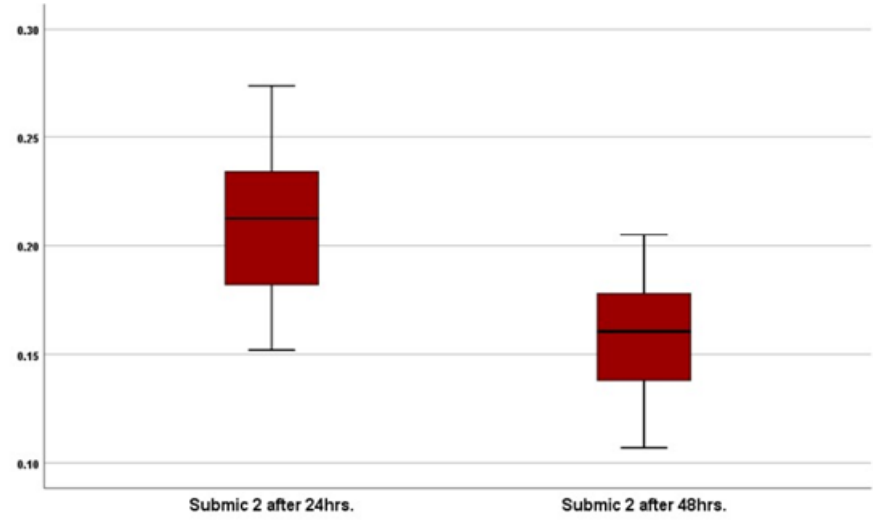

Figure 9: Means comparison of Submic 2 silver nanoparticles after 24 and 48 hrs. (n=50); paired t- test was used

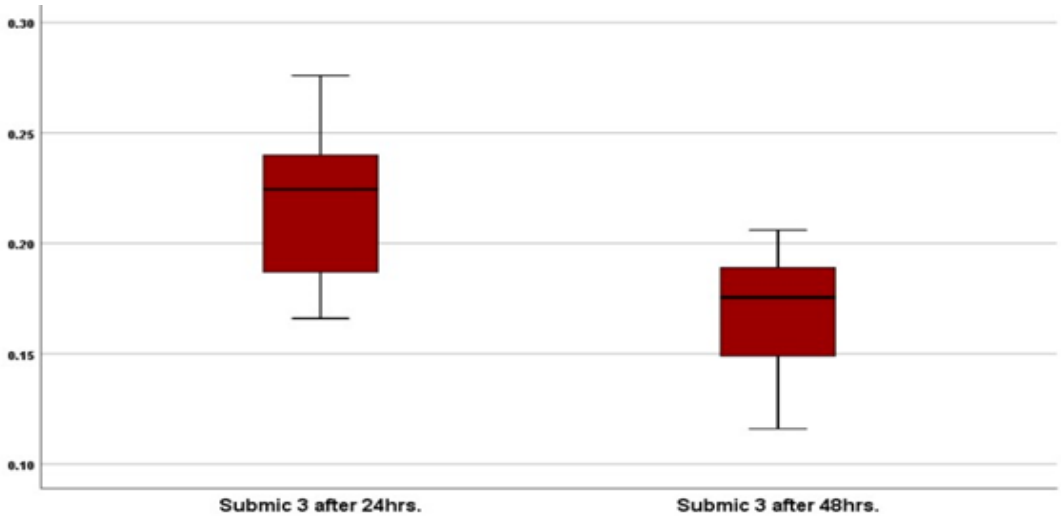

Figure 10: Means comparison of Submic 3 silver nanoparticles after 24 and 48 hrs. (n=50); paired t- test was used

Study patients

The incidence of *Salmonella* infection in Iraq is 44.25%, which is a very high percentage compared with the other countries especially in developed countries like the United States (0.015%) [17] as a result of the continuous exposure when traveling throughout the world among pet birds and reptiles [15].

Antibiotic susceptibility testing

Most of the isolates showed multiple resistance to antibiotics and presence of these patterns to more than one antibiotic is due to the repeated use of antibiotics as therapeutic materials without medical advice and/or resorting to sensitivity testing and may lead to the use of antibiotics in low doses compared with the prescribed doses due to the lack of complete special healing potions. Therefore, because *S. typhi* isolates became resistant to more antibiotics, drug sensitivity testing has become necessary for its correlation between spread and prevalence of *Salmonella* and the extent of its resistance to antibiotics [16].

Biological resistance is a common trait observed during our research, and this is consistent with a study that proves the multi-antibiotic resistance is that *S. typhi* strains have become a major problem in Asia, totally in agreement with (Pirtarighat *et al.*, 2019) [17].

Bac-SNPs biosynthesis

The bacteriocins use in the synthesis of bacteriocins-capped SNPs was validated by a shift in color from pale yellow to reddish-brown. This provided a preliminary indication of Bac-SNP synthesis [18].

Characterization of silver nanoparticles

The continued evolution of bacteria strains display the resistance to multiple antibiotics, and makes the operators to look for antimicrobial alternatives. Thus, silver which is commonly considered as a broad-spectrum antimicrobial agent could represent a suitable option, especially in its nanoform. There is circumstantial evidence that these particles have a good antimicrobial activity, AgNPs have shown antimicrobial activity against a wide array of microbes, probably due to their multiple mechanisms of antimicrobial action, including the activity against the drug-resistant bacteria [19].

Antibacterial activity by using of AgNPs

The prepared silver nanoparticles exhibited strong antimicrobial activity against *S. typhi* and "Minimal Inhibitory Concentration" was 1.9 µg/ml, while [20] agreed that reported the MICs of $AgNO_3$ were varied in the range of 0.09–0.3 µg/ml against *Pseudomonas aeruginosa*, who found that the anti-microbial activity of AgNPs against *S. typhi* is highest at the concentration of

1.9 µg/mL by using the well-diffusion method. Hence, this project was the first to deal with *S. typhi* by striking AgNPs. Therefore, a comparison was made with *Pseudomonas aeruginosa* to estimate MIC level of $AgNO_3$ versus *S. typhi*.

This comparison against *Pseudomonas aeruginosa* with antimicrobial properties of silver nanoparticles are well-established and several mechanisms for their bactericidal effects were produced and characterized for silver nanoparticles by *Lactobacillus spp.*, and also the determination of inhibitory effect was done against growth of pathogenic bacteria.

Determination of silver nanoparticles activity by agar wells diffusion assay (MIC), (Sub MIC)

The results of MIC and sub MIC tests revealed a higher MIC value for *S. typhi* compared with the other tested pathogens. This may be due to the differences in bacterial cell walls, since Gram-negative bacteria have the thinner cell wall compared with Gram-positive bacteria that was in agreement to [21], who reported that *S. aureus* was more resistant against nano silver than Gram-negative *S. typhi.* However, MIC values were identical for all the pathogens. It has been previously stated that bactericidal property of nanoparticles is dependent on the concentration and size of nanoparticles, and also the initial bacterial concentration silver nanoparticles with size of (1.9-500 µg/mL) was reported to be most effective against bacteria through the direct interaction with bacterial cells.

Conclusion

It is possible that AgNPs act similarly to the antimicrobial agents used for the treatment of bacterial infections, which show four different mechanisms of action including interference with cell wall synthesis, inhibition of protein synthesis, interference with nucleic acid synthesis, and inhibition of metabolic pathway.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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