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An Investigation of the Effect of Copper Oxide and Silver Nanoparticles on *E. Coli* Genome by Rapd Molecular Markers

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Abstract

Regarding the bacterial resistance of current antibiotics, many studies have been conducted to evaluate the antimicrobial properties of metal nanoparticles such as silver and copper oxide. This study was carried out to compare the effects of these nanoparticles on the genome of *Escherichia coli* strain O157: H7 as a model for gram-negative bacteria.

For this purpose, the bacteria were first treated by 30 and 60 µg/ml the nanoparticles and the growth of bacteria was controlled at certain time intervals by spectrophotometry to evaluate the antimicrobial activity. Then the DNA was extracted to investigate the effects of the nanoparticles on the genomes 4 hours after treatment using RAPD-PCR. The bands obtained from electrophoresis of PCR products on agarose gel 2% were analyzed.

The results of the study revealed that silver and copper oxide nanoparticles not only inhibit the growth of bacteria, but also change the genomic DNA sequences and cause genetic differences between control and treated samples. Metal nanoparticles are antibacterial compounds, and copper oxide was more effective than silver on *E. coli* genome as a model for gram-negative bacteria.

Keywords: Silver and copper oxide nanoparticles; Changes in DNA sequences; *Escherichia coli*; RAPD polymerase chain reaction (RAPD-PCR)

Abbreviations: EMB: Eosin Methylene Blue Agar; BHI: Brain Heart Infusion; OD: Optical Density; NDM-1: New Delhimetallo-Beta-Lactamase-1; RAPD-PCR: RAPD Polymerase Chain Reaction

Background

In general, antibacterial agents are classified into two categories: bactericidal and bacteriostatic (growth inhibitor). However, the widespread and indiscriminate use of anti-bacterial agents has been led to bacterial resistance, which is a serious challenge in this area. Resistance often affects different stages of development such as inheritance to new strains, which requires therapeutic strategies for diseases caused by bacteria [1]. Metal nanoparticles including copper and silver have antimicrobial effect against bacteria, viruses and other microorganisms [2]. Copper nanoparticles, especially inexpensive nanoparticles at the level of micro-electrical applications, have received more attention in recent years and are likely to be the latest discovered antimicrobial agents [3].

Unlike the usual chemical disinfections, antimicrobial nanomaterials are not expected to manufacture harmful disinfections [4]. Antibacterial effects of metal nanoparticles are because of very small size and high surface area to volume ratio, which allow being in contact directly with microbial membranes and releasing metal ions [5]. Targeted uses of silver and copper oxide nanoparticles with antimicrobial properties require more attention in terms of compatibility with the environment. Considering the fact that copper nanoparticles are lethal to other organisms, for example against crustaceans such as *Daphnia magna* and *Thamnocephalusplatyurus* and also *Pseudo- kirchneriella subcapitata* algae at low concentrations (3.2, 0.18 and <1 mg/l, respectively) reported in 2008 and 2009 [6,7] and thereby a degree of bactericidal of nanoparticles have been shown to aquatic organisms.

It has been also reported that low concentrations of silver ions released from silver nanoparticles are able to haemolysis of red blood cells, in vitro [8,9]. In addition, silver nanoparticles can directly affect the normal functioning of cells in the body, causing dysfunction of the organs [10]. As well, numerous reports and

laboratory studies have shown that silver nanoparticles can induce immune responses [11]. Several experimental researches have proved that silver nanoparticles cause damages to DNA and cells as well as result in cancer, oxidative stress and detoxification of metal [12,13].

Therefore, further investigations are required on nanoparticles to determine the effective concentrations of antibacterial and their genotoxicity effects as a suitable replacement for antibiotics and disinfectants. Since the antibacterial effects of silver and copper oxide nanoparticles have not been yet studied on the genomes; so this study was conducted to evaluate the effect of silver and copper oxide nanoparticles on the genome of *Escherichia coli* as a model for gram-negative bacteria and compare the effect of nanoparticles on the genome using random amplified polymorphic DNA- PCR (RAPD-PCR) technique.

Materials and Methods

Bacterial culture and the conditions

Characteristics of *Escherichia coli* 0157: H7 (ATCC 25922) bacteria was identified on eosin methylene blue agar (EMB) medium. The bacteria were cultured in 5 ml of the Brain Heart Infusion (BHI) broth, and were left overnight in a shaking incubator at 37°C at rpm 200. The growth rate of bacteria was controlled by measuring optical density (OD) of medium at a wavelength of 600 nm [14].

Evaluate the antimicrobial properties of copper oxide and silver nanoparticles

Copper oxide and silver nanoparticles less than 20nm in diameter were synthesized by the Nanotechnology South Korea. Characterization and analysis of the nanoparticles by electron microscopy have been presented in (Figure 1). Phosphate buffer saline (pH 7.4) was used as a solvent for preparing 30 and 60µg/ml concentrations of the nanoparticles, separately in tubes. The tubes were placed in a shaking incubator at 37°C at 200rpm and their OD was measured at 600nm with intervals of 2, 4 and 24 hours for the bacteria treated by nanoparticles to measure growth.

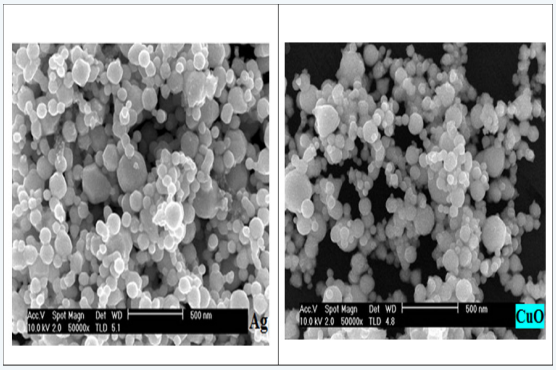

Figure 1: Microscopic images by SEM for Cuo and Ag nanoparticles.

DNA extraction and RAPD-PCR

DNAs of treated and control bacteria were extracted using DNA extraction kit (ExirAzma Co.) in accordance with the kit instructions, and then the quantity and quality were analyzed by spectrophotometry and electrophoresis on agarose gel 1%. RAPD- PCR molecular marker method was used to examine the effect of nanoparticles on bacterial genome. Initially, RAPD 10 bases-primers (Cinnagene Co.) were prepared to perform RAPD-PCR method. Sequences and characterization of primers have been shown in (Table 1).

Table 1: Sequences of primers.

The nucleotide sequence of primer	The name of the primer
OPR12	ACAGGTGCGT
OPS11	AGTCGGGTGG
OPA11	CAATCGCCGT
OPS.13	GTCGTTCCTG
OPS-09	TCCTGGTCCC
OPA10	GTGATCGCAG
OPB-7	GGTGACGCAG
OPQ-14	GGACGCTTCA
OPT14	AATGCCGCAG
OPS14	AAAGGGGTCC
OPA09	GGGTAACGCC
OPS05	TTTGGGGCCT
OPD04	TCTGGTGAGG
OPT17	TCTGGTGAGG

Ingredients listed below at concentrations of 25ml volume were prepared for PCR reaction to amplify samples; 1µl primer, 2.5µl (10 x) PCR buffer, 3µl MgCl2, 1µl dNTP mix, 1µl of extracted DNA samples and 0.3µl of DNA Taq polymerase that was reached to the volume of 25ml by 16.2µl of deionized distilled water.

The mixture was placed in a thermocycler (Corbett research, Australia) with the following schedule: the initial template DNA denaturation at 95°C for 5 minutes, followed by 40 cycles of PCR reactions, so that 95°C for 35 seconds for denaturation of template DNA strands, 30°C for 45 seconds to attach the primers to the template strand, 72°C for 45 seconds for the polymerization of a new strand from template strand. 7 minutes were required to complete the polymerization of incomplete strands. These compositions and the temperature profiles after optimizing the PCR conditions were used for all 14 primers.

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Evaluation the results of RAPD-PCR

After completion of the PCR reaction, electrophoresis was done for 10µl of PCR products on agarose gel 2% (the size of 14×26cm) containing red safe in TBE buffer (1x) for 4 hours with a voltage of 120 volt to detect appeared bands; DNA ladder marker with 100bp was used to determine the product size and the images of gel were taken using imaging system (Uvitec, France).

Analysis of data obtained from electrophoresis

The bands resulting from analyzed RAPD were scored based on the presence or absence, respectively, as one and zero. The data was then entered into the software based on molecular weight; the similarity matrix was calculated by Dic and dendrogram were derived by UPGMA method in NTSYS-PC software.

Results

SEM electron microscopes were used for study of the copper oxide and silver nanoparticles (Figure 1).

Evaluate the antimicrobial properties of copper oxide and silver nanoparticles

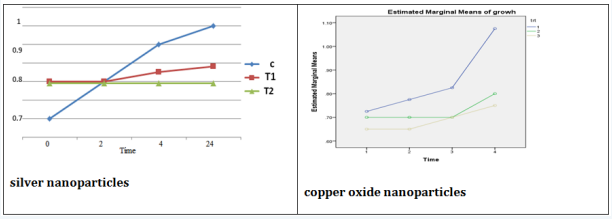

Figure 2: Growth curve related to control and bacteria treated by Cuo and Ag nanoparticles nanoparticles at different times.

The results of experiments on antimicrobial activities of copper oxide and silver nanoparticles against *Escherichia coli* bacteria have been presented in (Figure 2), demonstrating that the growth of bacteria was clearly stopped after treatment by nanoparticles in intervals of 2 and 4 hours and they had only minor growth after 24 hours.

RAPD- PCR product analysis

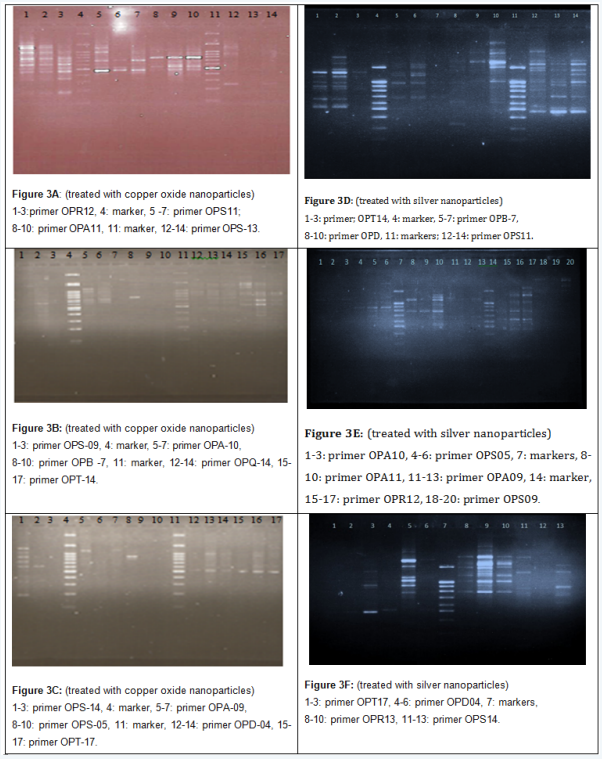

Figure 3: Agarose gel electrophoresis of PCR products treated with copper oxide (A- C) and silver (D- F) nanoparticles.

Table 2: Sequences of primers.

The name of the primer	copper oxide nanoparticles		silver nanoparticles	
	The number of bands formed	The difference between the control and treatment of bonds formed	The number of bands formed	The difference between the control and treatment of bonds formed
OPR12	9	4	7	4
OPS11	6	3	7	5
OPA11	6	4	6	5
OPS.13	3	3	6	2
OPS-09	2	2	2	2
OPA10	5	5	2	1
OPB-7	1	1	4	4
OPQ-14	3	2	6	6
OPT14	7	7	8	7
OPS14	5	5	5	5
OPA09	1	1	3	3
OPS05	2	2	5	4
OPD04	2	2	8	8
OPT17	1	0	4	4

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Table 3: Similarity matrix for samples treated with Cuo and Ag nanoparticles and control.

Dice (Czekanowski or Sorenson) Measure			Case
3:t60	2:t30	1:ctr	
		1.000	1:ctr
	1.000	0.5000	2:t30
1.000	0.4950	0.4530	3:t60

silver nanoparticles

Dice (Czekanowski or Sorenson) Measure			Case
3:t60	2:t30	1:ctr	
		1.000	1:ctr
	1.000	0.529	2:t30
1.000	0.703	0.451	3:t60

copper oxide nanoparticles

Electrophoretic bands obtained from amplification of 14 primers by the RAPD- PCR have been shown in (Figure 3) for bacteria treated by copper oxide and silver nanoparticles. The bands obtained from analyzed RAPD were scored based on the presence or absence, respectively, as one and zero. The conclusion was based on the difference in the bands formed by each primer, for control and treated samples (Table 2) as can be seen in (Table 2), totally 53 bands were produced for bacteria treated with copper oxide nanoparticles from 14 primers that 41 bands were different between the control and treated samples. Collectively 73 bands were also appeared for bacteria treated with silver nanoparticles which 60 bands were different between the control and treated samples.

(Table 3) shows the results of NTSYS-PC software in order to compare genetic variations between control and treated samples.

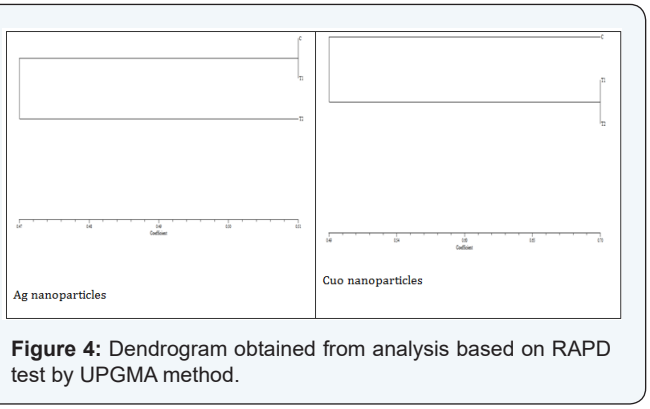

Figure 4: Dendrogram obtained from analysis based on RAPD test by UPGMA method.

The dendrogram was drawn by UPGMA in NTSYS-PC software to compare genetic variations between control and samples treated with nanoparticles. As seen in (Figure 4), control and samples treated with copper oxide nanoparticles have been located in two separate main branches, suggesting a genetic difference; but the control and first treatment of silver nanoparticles in a branch, and the second treatment in a separate main branch, reflecting the impact of nanoparticles at high concentrations.

Discussion

The development of severe bacterial resistance to antibiotics is a major health problem. In this regard, the nanoparticles are considered new antimicrobial agents [15]. Various industries and human daily life have been changed with the advent of nanotechnology. Antimicrobial potential of nanoparticles has attracted the attention of researchers and industrialists, which nanoparticles can be used as an alternative to antibacterial agents and antibiotics, as it is predicted that bacteria cannot become resistant to nanoparticles because nanoparticles can be effective on different parts and various enzymes, which this issue is confirmed by research of Sondi et al. [16] in 2004 on the antimicrobial activity of silver nanoparticles. They argued that antimicrobial activity of silver is carried out by blocking the electron transport system, changing the bacterial membrane function and inhibit the DNA replication. Silver ions are known to particularly inhibit thiol group-containing enzymes and proteins and thereby this mechanism plays an essential role in the antimicrobial activity of silver ions, although other cellular factors such as hydrogen bonds may also be involved [16].

New Delhi metallo-beta-lactamase-1 (NDM-1) is an enzyme that makes bacteria resistant to a broad range of beta-lactam antibiotics.Most isolates with NDM-1 enzyme are resistant to all standard intravenous antibiotics for treatment of severe infections [17]. DNA gyrase enzyme in *E.coli* participates in several important processes, and thus is physiological target for a series of antibiotics. *E.coli* mutants resistant to the two classes of drugs have provided important evidences about subunit structure of the enzyme.

Drug resistance is controlled by two groups of genes (gyr A and gyr B) that are structural genes for subunits of the enzyme [18,19]. Therefore, the nanoparticles can be used for antimicrobial activities.But both advantages and disadvantages need to be considered in the host cell. Nanoparticles arenot toxic to cells in the body at low concentrations.In this study, certain concentrations of silver and copper oxide nanoparticles were used for bacterial treatment to find out antimicrobial properties. The results of the present study (Figure 1) showed that the nanoparticles with diameters less than 20nm in doses of 30 and 60µg/ml had relatively good antimicrobial effects so that were able to almost inhibit the growth of all bacteria in the samples.

According to numerous studies that have demonstrated the effect of silver and copper oxide nanoparticles as antimicrobial agents [16,20-25], the main purpose of this research was to evaluate and compare the effect of nanoparticles on bacterial genome at the lowest effective dose.Reports have been also presented based on the nanoparticles effects on bacterial genome which can induce DNA single-strand breakage and affect gene expression [26].

Li et al. [26] in 2012 during a study stated that silver nanoparticles are imported into bacterial cells and influence on the DNA twisting, thus inhibit the replication and cell

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proliferation. The silver nanoparticles are combined with the thiol groups in respiratory enzymes and inhibit respiration process in bacterial cells [27,28] or as expressed in previous studies, metal oxide nanoparticles may interfere with the transcription and translation [29].

This study was also conducted to investigate the effects of silver and copper oxide nanoparticles on the genome of *Escherichia coli* strain O157: H7 as a model for gram-negative bacteria. In this regard, based on the RAPD-PCR reaction with 14 primers, the presence or absence of bands in the gel images (Figure 3) suggest changing the DNA sequence by silver and copper oxide nanoparticles. A large number of primers failed to detect target sequences, and therefore the related segments were unable to replicate and we have seen the absence of bands on the agarose gel.

The difference among the bands observed in the treated and control groups of bacteria suggests that the target sequences of primers have been changes in the treated bacteria that make a difference in binding of primers and PCR amplification. The genomic sequence variations could possibly be in the process of replication.

It can be concluded that a change in the base pairing properties could be one of the possible causes of DNA sequence variations due to treatments of bacteria by silver and copper oxide nanoparticles which during the replication can lead to change the sequences in daughter strands. Also, silver nanoparticles could possibly cause dysfunction in DNA pol enzyme and are able to target the molecular mechanisms of replication accuracy which is involved in the synthesis of new strands based on the structure of Watson and Crick, changing the sequence of daughter strands [30].

Variations observed in DNA sequence in this study could also be a factor for growth inhibition and cell cycle through the occurrence of mutations, followed by gene expression changes associated with growth and cell cycle control [31]. Copper oxide and silver nanoparticles inside the cells can release ions of copper oxide [30,31] and silver, which react with DNA phosphorus and then disable the replication.

Silver ions increase the level of ROS, react with the sulfur-containing proteins and inhibit the respiratory enzymes, resulting in cell death [31,32]. The energetic ions of copper cations with moving easily among the lipid layers are trapped by the cells which produce a specific reaction of oxygen, penetration of lipid peroxidation and protein oxidation.

Cell wall components are responsible for binding with copper nanoparticles. Amine and carboxyl groups of peptidoglycan participate in copper process and cell wall damages [33]. Accordingly, given that growing and replicating bacteria in the present research have been treated with silver and copper oxide nanoparticles, it could be argued that these nanoparticles most likely can create disruption in replication as well as in repair mechanisms to cause multiple mutations in DNA sequences.

In accordance with the results of (Figure 1) there are significant differences between treatment and control samples and in fact bacteria were separated into two distinct strains in terms of genome. Based on dendrogram, samples of control and treated with copper oxide nanoparticles by being in separate categories demonstrate great genetic distances. But the control and first treatment of silver nanoparticle were placed in single branch, and the second treatment was subjected to a separate main branch, reflecting the impact of nanoparticles on bacterial genome at high concentrations. Therefore, according to previous studies and the current research, it can be concluded that the nanoparticles can reduce the expression of genes involved in cell cycle control by creating mutations in their sequences, and thus reduce the growth of bacteria.

Conclusion

The results of this study and similar findings indicate the proper efficacy of nanoparticles as antibacterial compounds, but copper oxide nanoparticles compared with silver nanoparticles was more effective on E. coli genome as the model for gram-negative bacteria and since the copper nanoparticles are less expensive, thus is cost-effective as antibacterial agents. But because the nanoparticles can bind with DNA, so in the long term can make hard mutants and have adverse effects on eukaryotic host cells and it is impossible to be tested in a short time. But it is suggested to be further investigated in future works on the effects of nanoparticles in eukaryotic cells, which the nanoparticles can be used in various industries with greater certainty.

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