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Antibacterial activity of nanoparticles of titanium dioxide, intrinsic and doped with indium and iron

Natividad Castro-Alarcón[1]*, José Luis Herrera-Arizmendi[1], Luis Alberto Marroquín-Carteño[1], Iris Paola Guzmán-Guzmán[1], Armando Pérez-Centeno[2] and Miguel Ángel Santana-Aranda[2]

[1]Laboratorio de Investigación en Microbiología, Facultad de Ciencias Químico Biológicas, Universidad Autónoma de Guerrero. Chilpancingo, Gro., Mexico.
[2]Departamento de Física, Centro Universitario de Ciencias Exactas e Ingenierías. Universidad de Guadalajara, Guadalajara, Jal. Mexico.

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ABSTRACT

The need for new antimicrobial compounds has drawn attention on developing new and emerging materials based on nanoparticles with antimicrobial activity. The aim of this research was to evaluate the antibacterial activity of nanoparticles of titanium dioxide, intrinsic and doped with Indium and Iron in *Escherichia coli* and *Staphylococcus aureus*. The bacteriostatic effect of $Ti0_2$ nanoparticles (two samples), $Ti0_2$:Fe and $Ti0_2$:In with concentrations of 50, 250 and 500 µg/ml, was observed by optical density measurements. The bactericidal effect was determined by plate count agar Muller-Hinton, where they incubated for 12 h: 50 µl of bacterial suspension (concentration 1.5×10^6 bacterium/ml), con 50 µl of nanoparticles suspended at concentrations between 39 and 2500 µg/ml. Then, to 10^{-6} dilutions were made and plated on agar for colony counts. There were significant decreases in the bacterial optical densities with respect to control, using TiO_2 nanoparticles prepared with different contents of acetic acid at concentrations of 250 and 500 µg/ml versus *E. coli* and *S. aureus*. In the plate counts, there was a significant reduction in the number of CFU of *E. coli* using TiO_2 nanoparticles (50% AcAc) in concentrations 39 to 2500 µg/ml; in the case of *S. aureus* decrease seen in concentrations 78 to 2500 µg/ml. In both bacteria, we observed decreased bacterial growth with TiO_2 nanoparticles at concentrations of 156 to 2500 µg/ml. The two variants of preparing TiO_2 nanoparticles have higher intrinsic activity against *E. coli* and *S. aureus*, while nanoparticles doped with Indium and Iron, could not overpower the antibacterial effect.

Keywords: Titanium oxide, nanoparticles, antibacterial activity.

*Corresponding author. E-mail: natividadcastro24@gmail.com. Tel: 52 (7474725503. Fax: 52 (7474725503.

INTRODUCTION

The term nanoparticles (NP) is used to define particles smaller than 100 nm in diameter, which originate from two sources: primary (natural) and secondary or artificial (synthesized compounds), which may be organic or inorganic (Kaluza et al., 2009; Sanvicens and Marco, 2008; Buzea et al., 2007). As NP become smaller, the percentage of surface atoms increases in relation to the total number of atoms (Li and Zeng, 2011), its properties change considerably and have a melting point lower than that of a larger mass of the same composition (Grande, 2007).

Actually, the nanoparticles are used in various areas such as medicine, pharmaceuticals, textiles and the electronics industry with the purpose of improving the quality of life (Tsuzuki, 2009). Because of its photocatalytic activity they are used in the separation of water, energy production, air and water purification, sterilization of surfaces, synthesis of organic compounds and in the reduction environmental pollution. NPs are used in medicine as metal oxide for coating of biomedical devices, such as prostheses, to prevent bacterial colonization and proliferation, with its catalytic activity (photo) (Visai et al., 2011). Also, NPs are applied for the preparation of drugs, protein detection and pathogen,

treatment of tumors, separation and purification of biological molecules and cells (Wang et al., 2011).

Organic NPs have been used as bactericides, but its antibacterial properties are reduced at high temperatures (Rezaei-Zarchi et al., 2010) and the inorganic type may have a general mechanism of toxicity against bacteria (Taylor and Webster, 2011).

One of the materials used in the last decades is titanium dioxide (TiO_2) because it is not toxic, is easy to produce and cheap (Xie et al., 2009). The morphological properties of titanium dioxide NPs greatly influence their applications (Yan et al., 2005). TiO_2 (occurs in nature) in three different forms: rutile, anatase and brookite. Of the three structures mentioned, anatase NPs are the most commonly used for photocatalysis. TiO_2 nanomaterials are of interesting in a wide range of applications such as photocatalysis, dye sensititized solar cells, gas sensors, photochromic devices, photo degradation of organic compounds, deactivation of microorganisms, organic synthesis and cells culture (Banerjee, 2011).

Metals such as platinum (Pt), silver (Ag), gold (Au), nickel (Ni) and copper (Cu) have been added to TiO_2 NPs. These combinations have been very effective in improving photocatalysis(Gupta and Tripathi, 2011). TiO_2 NPs combined with silver (Ag) in the presence of UV light have been showing greater effect against the growth of *E. coli* compared with TiO_2 NPs without Ag (Ashkarran et al., 2011).

The inhibitory activity of NPs generally can be along two main pathways that are related to each other and in many cases occur simultaneously: 1) disruption of membrane potential and integrity and 2) production of reactive oxygen species (ROS), also known as oxygen-free radicals, the NPs acting as nanocatalysts (Beyth et al., 2015). The membrane damage occurs when NPs electrostatically bind to the bacterial cell wall and membranes, leading to alteration of membrane potential, membrane depolarization and loss of integrity which, in turn, results in an imbalance of transport, impaired respiration, interruption of energy transduction and/or cell lysis, and eventually cell death. The distortion of the cell structure and expansion could cause destabilization of the membrane and increase membrane fluidity, which in turn increases the passive permeability and is manifested as a leak of several vital intracellular components such as ions, ATP, nucleic acids, sugars, enzymes and amino acids (Díaz-Visurraga et al., 2011).

The free radicals are induced indirectly due to respiratory chain disruption or directly by NPs themselves. A burst of ROS causes, via severe oxidative stress, damage to the all the cell's macromolecules, leading to lipid peroxidation, alteration of proteins, inhibition of enzymes, and RNA and DNA damage. At high concentrations, the ROS leading to cell death and low doses cause severe DNA damage and mutations (Beyth et al., 2015). In some cases where ROS production is induced by visible or UV light, toxicity of the particles is photocatalytic (Park et al., 2006). It was observed that the TiO_2 NP combined with Ag plus UV light can be used for sterilization of vegetative cells of *Bacillus*, while TiO_2 nanoparticles in the presence with UV light are effective against spores (Thi Tuyet Nhung et al., 2012).

In the present investigation the antimicrobial activity of nanoparticles of titanium dioxide intrinsic and doped with indium and iron was evaluated, against Gram-positive and Gram-negative pathogenic bacteria to assess the possibility of them being used as a new antibacterial strategy and environmental health.

MATERIAL AND METHODS

Nanoparticles

TiO_2, TiO_2:In and TiO_2:Fe nanoparticles were prepared by the Sol-Gel technique without reflux, using a mixture of titanium propoxide, acetic acid and Tween80® on propanol, with the following molar proportions 4:24:1:180; based on the results of the synthesis of Choi et al. (2006). For doping with indium and iron we used in appropriate amounts $InCl_2$ and $FeCl_3$ in propanol, for obtaining 0.5% and 1% indium and 1.25% iron of the titanium ions. Also, a sample prepared with half the amount of acetic acid (50% AcAc), that is to say 4:12:1:180. The solutions were stirred without reflux, up to the point that they became almost solid, from solvent evaporation. After drying in air at 200°C for 2 h and calcined in air at 400°C for 8 h in a muffle furnace (Barnstead 1100). Samples were observed in Field Emission Scanning Electron Microscope (Mira3, TESCAN), working at 30 kV and using secondary electrons detector. The powders obtained were ground in an agate mortar and reserved for tests of antibacterial activity. For comparison we used commercial TiO_2 (Degussa P25).

Antibacterial activity

Bacterial growth curves were performed in order to observe the effect of different nanoparticles on strains of *E. coli ATTC 25922* and *Staphylococcus aureus ATCC 29213*, growth following a 12 h interval. The strains were seeded in MacConkey agar and mannitol salt agar respectively and incubated at 37°C until colonies have visible. From one or two colonies of bacteria suspended in 3 ml of 0.9% saline solution prepared to a concentration of 0.5 McFarland (1.5×10^8 bacterial cells/ml). The flasks were prepared for each layer containing 20 ml of nutrient broth with concentrations of 0, 50, 250 and 500 µg/ml of TiO_2 of nanoparticles, respectively. The flasks were inoculated with 100 µl of the bacterial suspension of each strain and incubated at 37°C under continuous stirring to 250 r.p.m. for 24 h. The optical density (O.D) of the cultures at 600 nm, an initial determination and readings every 2 h was measured for 12 h to monitor bacterial growth (Rezaei-Zarchi et al., 2010).

Plate count

Bactericidal activity was evaluated and nanoparticles in bacterial strains were tested in bacterial growth curves, to determine the number of bacterial colonies growing with different concentrations of nanoparticles. From a dilute suspension 1:100 concentration of 0.5 McFarland nephelometer (1.5×10^8 bacteria), 50 µl of this dilution was incubated in Eppendorf tubes, mixed with 50 µl of suspensions of nanoparticles of TiO_2, TiO_2 (50% AcAc) and P25 at

concentrations of 39 to 2500 µg/ml and incubation at 37°C for 12 h, during this time the tubes were shaken every hour in vortex. To perform the plate count preparations were diluted to 10^{-6} and plated on Mueller Hinton agar. After incubation for 24 h colony counting was performed, the results of which were multiplied by the dilution factor to obtain the total number of CFU per 100 ml.

Statistical analysis

Experiments were performed in triplicate. Statistical analysis was performed using STATA v.12.0 software, determining mean and standard deviation of the O.D determined between repetitions of the experiments; also p values were determined using the student t-test between different experimental groups over control. The graphics were made in the program GraphPad PRIMS.

RESULTS

Synthesized and commercial TiO_2 nanoparticles were characterized by x-ray diffraction and Raman spectroscopy. All synthesized nanoparticles have anatase crystalline phase. The presence of oxides of the doping elements (Fe and In) was not observed by X-ray diffraction nor Raman spectroscopy. This could mean that doping elements were most likely incorporated within the TiO_2 lattice; either interstitially or substitutionally. The average crystallite sizes were calculated from diffraction patterns using Scherrer's equation; resulting 12 nm for TiO_2, 8.5 nm for TiO_2:In (1%), 10.5 nm for TiO_2:In (0.5%), 8.5 for TiO_2:Fe (1.25%), 7.9 for TiO_2-AcOH (50%) and 21 nm for P25. The nanoparticles synthesized shown in Figure 1. Antibacterial activity of 6 samples of TiO_2 nanoparticles were evaluated on the growth of *E. coli* ATCC 25922 and *S. aureus* ATCC 29213 in liquid medium. The decrease in O.D of experimental cultures (nanoparticles/bacteria) from the control cultures (bacteria without nanoparticles) was the indicator of the effect of nanoparticles. The following conversion factors of O.D was used CFU/ml: 1 $O.D_{600nm}$ *E. coli* = 1×10^9 CFU/ml (Chang et al., 2013) and 1 $O.D_{600nm}$ *S. aureus* = 1.5×10^8 CFU/ml (Ausubel et al., 2002).

In Figure 2 the bacterial growth of *E. coli* ATCC 25922 and *S. aureus* ATCC 29213 is observed in the presence of TiO_2 NPs. *E. coli* had a decrease of optical density in the exponential phase between 4 and 6 h using concentrations of 250 and 500 µg/ml, and which became more evident after 6 h of growth. For *S. aureus*, using concentrations of 50, 250 and 500 µg/ml showed an altered decreasing growth between 4 and 8 h.

With the nanoparticles of TiO_2 (50% AcAc), we observed an antibacterial effect on *E. coli* using concentrations 250 and 500 µg/ml in the exponential phase between 4 and 8 h of growth. While for *S. aureus* only with concentrations of 500 µg/ml was noticeable with antibacterial activity between 6 and 12 h of growth. With commercial nanoparticles Degussa P25, a decrease in optical density of *E. coli* and *S. aureus* between 4 and 6 h of growth was observed using the three concentrations, but the effect was greater at concentrations of 250 and 500 µg/ml compared with TiO_2 prepared in this study.

By employing doped nanoparticles of TiO_2:In (1%), TiO_2:In (0.5%), TiO_2:Fe (1.25%) there was no significant decrease in optical density with the three concentrations used for *E. coli*. However, a significant decrease was observed in *S. aureus* at concentrations of 500 µg/ml of the nanoparticles of TiO_2:In (0.5%).

In order to compare the antimicrobial effect of nanoparticles studied using growth curves, *p* value were calculated. The effect of the nanoparticles at a concentration of 500 µg/ml showed antibacterial activity, which was more evident in nanoparticles of TiO_2, TiO_2 (50% AcAc) and P25, a significant value ($p < 0.05$) in *E. coli*. The concentration of TiO_2:In (0.5%) also had an effect on *S. aureus* (Figure 3).

The bactericidal activity of the nanoparticles in the studied bacterial strains was determined by the bacterial colonies growing number being challenged at different nanoparticles concentrations. We counted in a range of 30 to 200 colonies by dilutions made. In controls without nanoparticles of *E. coli* and *S. aureus,* we determined 179×10^8 CFU/ml; compared with viable counts of various concentrations of nanoparticles and obtained the p value. Table 1 shows the significant effect of different NPs concentrations on the growth for *E. coli*, the P25 commercial nanoparticle showed significant effect ($p < 0.05$) at all concentrations. The significant effects of NPs on the growth against *S. aureus* are shown in table 2.

DISCUSSION

Actually the search for new alternatives for application in biomedicine such as the elimination of bacterial infections, mainly nosocomial type, has caused a significant interest in the development of nanomaterials with antimicrobial capacity. During this study the intrinsic antibacterial properties of TiO_2 nanoparticles were evaluated and doped TiO_2:Fe and TiO_2:In at different concentrations to determine which presented the best antibacterial activity against the growth in culture of *E. coli* (ATCC 25922) and *S. aureus* (ATCC 29213); used as test organisms for conducting experiments.

Carrying out growth in a liquid medium helped us to evaluate the bacteriostatic effect of various nanoparticles. The most significant results were obtained on both strains using TiO_2 and TiO_2 (50% AcAc) nanoparticles at concentrations of 500 mg/ml. The quantitative test plate count allowed us to estimate the antibacterial activity through the survival ratio calculated from the number of viable cells which formed colonies on Muller Hinton agar plates (CFU µg/ml). The results were relevant to the two intrinsic synthesized nanoparticles that were used TiO_2 and TiO_2 (50% AcAc).

TiO_2 nanoparticles (50% AcAc) showed the best antibacterial activity; even surpassing control nanoparticles, when using these nanoparticles, smaller

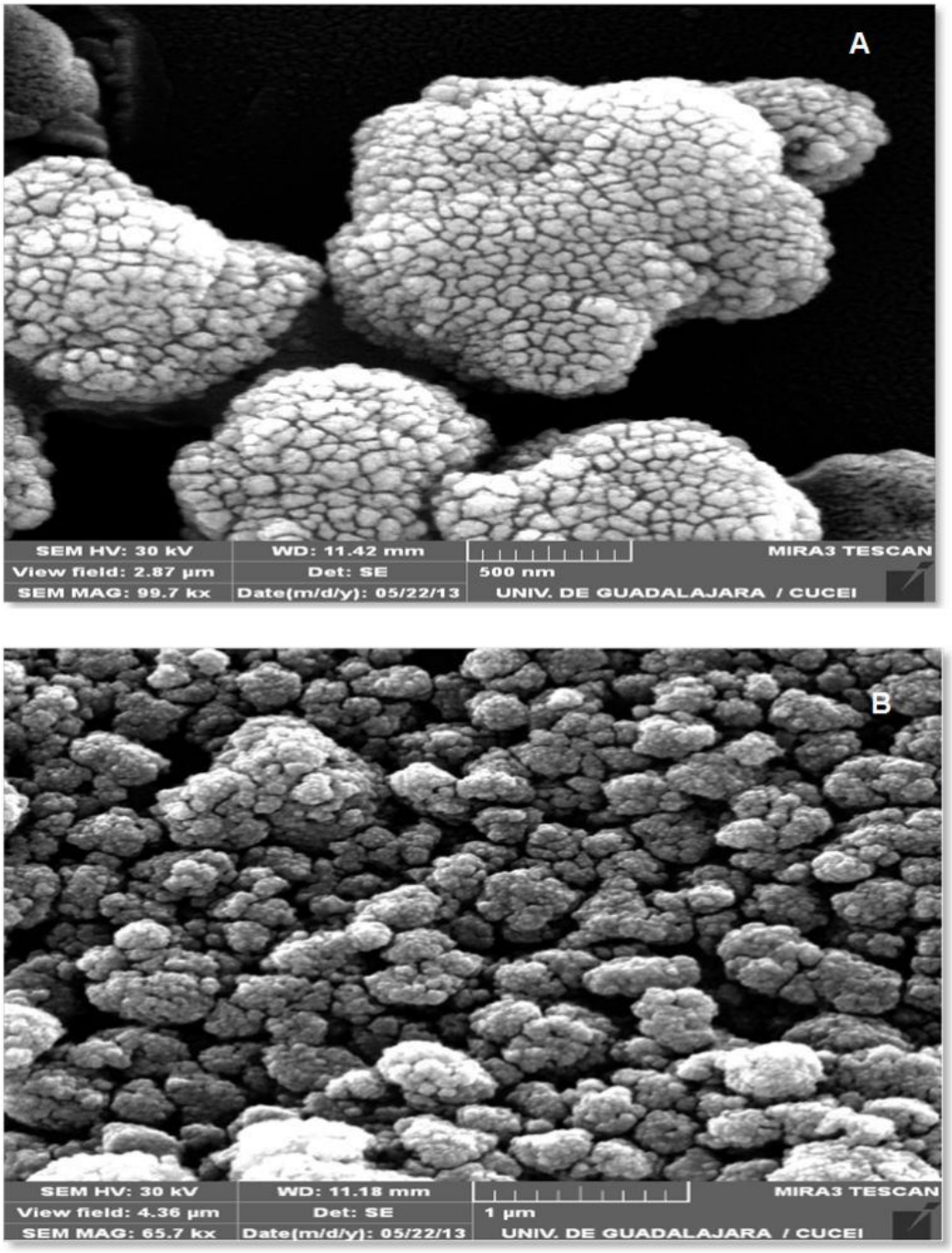

Figure 1. A) Nanoparticles of TiO_2; and B) Nanoparticles of TiO_2 (50% AcAc).

amounts CFU/ml were obtained. This shows that it has a greater bactericide effect on the bacterial species, a fact which can also be directly related to the percentage of acetic acid used in the synthesis of these nanoparticles. The use of 50% acetic acid favored the bactericide effect of TiO_2 unlike doping of TiO_2 nanoparticles with iron and indium. In a study by Enríquez et al. (2008), a synthesis of TiO_2 nanoparticles were made, with varied amounts of acetic acid to analyze the physicochemical properties of nanoparticles and it was found that when using 1,125 ml of acetic acid the nanoparticles reached a size of 7.2 nm, smaller than the 16 nm commercial nanoparticles. Therefore, the amount of acetic acid influences nanoparticles size.

It should be noted that compared to bacterial growth in liquid medium in the presence of TiO_2 and TiO_2 nanoparticles (50% AcAc) in 3 different concentrations (50, 250 and 500 µg/ml), lower growth was observed in

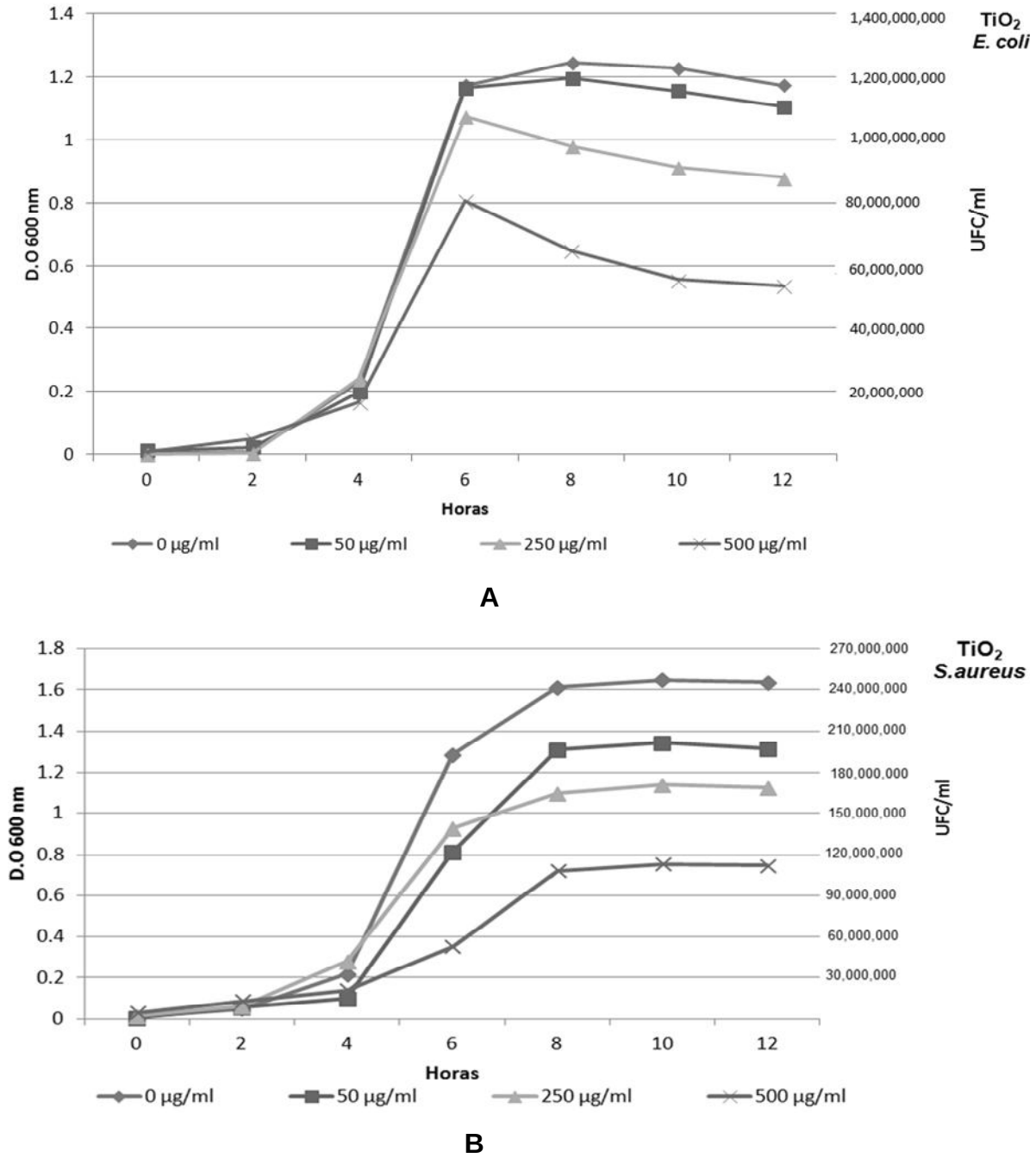

Figure 2. Bacterial growth with different concentrations of nanoparticles TiO_2. (A) *Escherichia coli* ATTC 25922, (B) *Staphylococcus aureus* ATCC 29213.

E. coli than *S. aureus*. This indicates increased resistance of the latter due to the large amount of peptidoglycan that it has, which gives greater protection; whereas *E. coli* has only a thin layer of peptidoglycan and lipopolysaccharide allowing greater interaction of the nanoparticles with these bacterial components.

The antibacterial activity of the nanoparticles used may be related to the binding of the nanoparticles to the outer membrane of *E. coli* causing inhibition of active transport and eventually inhibiting RNA, DNA and protein synthesis, leading to cell death. Research has been conducted indicating the possible mechanisms involved in the interaction of nanoparticles with biological macromolecules, which indicates that bacteria have a negative charge, while the metal oxide nanoparticles have a positive charge. This causes an attraction between bacteria-nanoparticles and leads to oxidation of the bacteria. The nanoparticles react with the thiol group

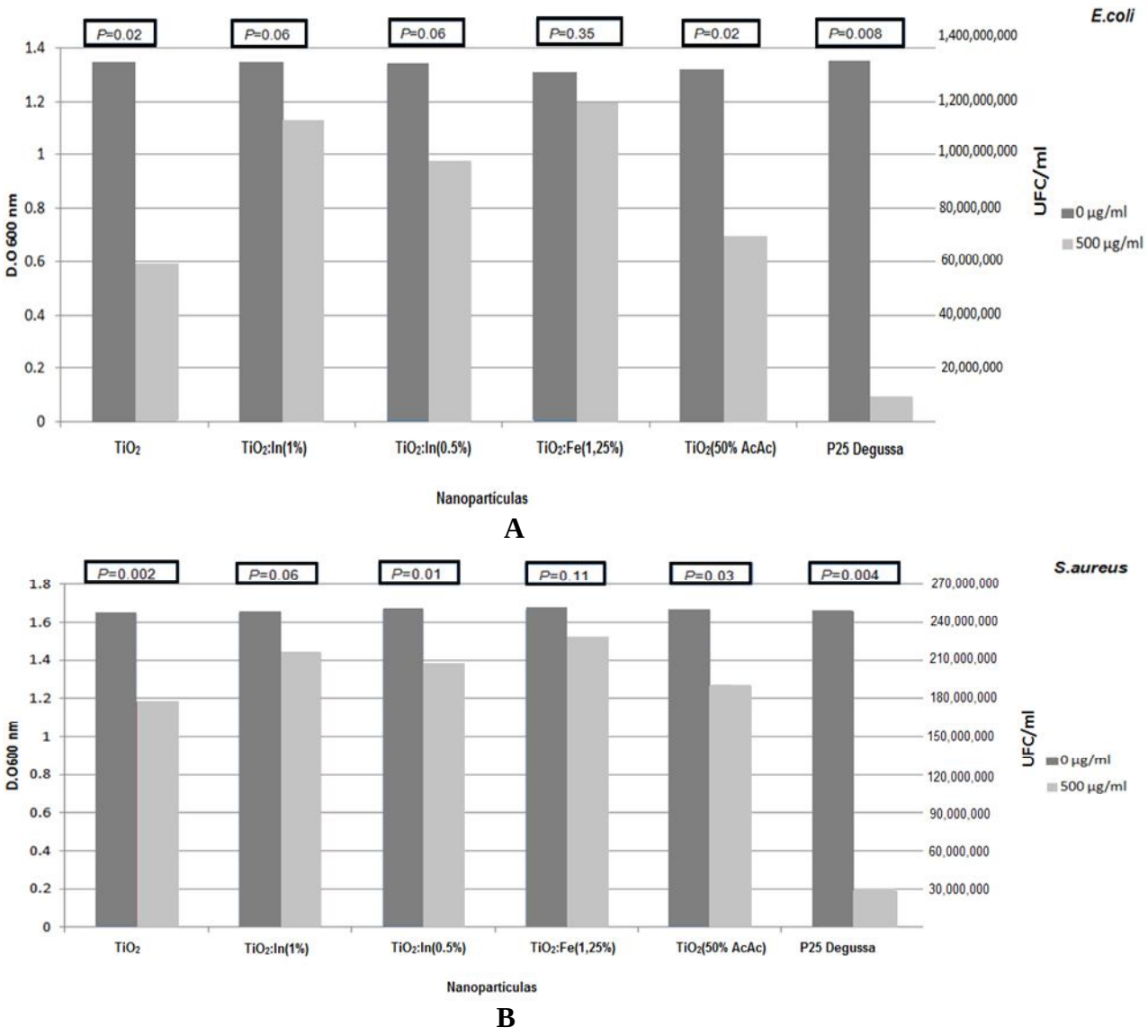

Figure 3. Optical density and Colony Forming Units/ml of bacterial growth after 12 h incubation with a concentration of 500 µg/ml, of intrinsic and doped nanoparticles. A) *Escherichia coli* ATTC 25922 and B) *Staphylococcus aureus* ATCC 29213.

(-SH) of the proteins in the bacterial cell wall, causing inactivation of transport proteins nutrients, reducing cell permeability and causing death (Zhang and Chen, 2009).

These mechanisms of action are proposed as being responsible for the antibacterial activity of the NP which is analyzed in this paper. Most researchers have demonstrated so far the mechanism of photocatalytic elimination of different microorganisms using titanium dioxide with UV or sunlight. This is the only mechanism of action resulting in the loss of structural integrity of the cells membranes in the presence of TiO_2 nanoparticles, although lipid peroxidation by the release of reactive oxygen species such as hydroxyl radicals and superoxide has also been proposed (Allahverdiyev et al., 2011).

The results obtained in this study are compared with two studies; the first made in 2010, for Reazaei-Zarchi et al., which determine the antibacterial activity of TiO_2 nanoparticles against *E. coli*, without the presence of UV rays, using concentrations of 500 and 1000 µg/ml; obtaining a value of $p < 0.05$ at these concentrations. This result was the same as that obtained in the present work, since a significant bacterial reduction ($p = 0.02$) was observed with TiO_2 nanoparticles at a concentration of 500 µg/ml against the same bacteria.

A second study by Mohammed Sadiq et al. (2010) where the effect of TiO_2 nanoparticles on the growth of *E. coli*, *Pseudomonas aeruginosa* and *Bacillus subtilis* was studied, mentions that at a concentration of 100 µg/ml there was an inhibitory effect for 3 bacteria, because logarithmic growth phase showed a marked decrease in

Table 1. Values of p plate count against *E. coli.*

Nanoparticle concentration (µg/ml)	TiO_2 p-value	TiO_2 (50% AcAc) p-value	P25 p-value
2500	0.0118	0.0055	0.0055
1250	0.0131	0.0089	0.0089
625	0.0232	0.0097	0.0097
312.5	0.0259	0.0146	0.0146
156.25	0.0406	0.0187	0.0187
78.125	0.0515	0.0240	0.0240
39.062	0.0760	0.0374	0.0374

Table 2. Values of p plate count against *S. aureus.*

Nanoparticle concentration (µg/ml)	TiO_2 p-value	TiO_2 (50% AcAc) p-value	P25 p-value
2500	0.0133	0.0095	0.0026
1250	0.0148	0.0102	0.0029
625	0.0202	0.0150	0.0031
312.5	0.0315	0.0165	0.0135
156.25	0.0489	0.0251	0.0119
78.125	0.0752	0.0435	0.0202
39.062	0.1257	0.0552	0.0374

bacterial optical density, similar to the effect observed in this work on *E. coli*, but at concentrations of 250 and 500 µg/ml.

In the case of the nanoparticles doped with Indium (0.5 and 1%), there was decrease in antibacterial activity. In Martínez and Gómez (2011), it is mentioned that there must be an optimum doping in the synthesis of nanoparticles that causes a phase transition from anatase to rutile, resulting in a decrease in the size of these nanoparticles and promoting their properties. So it is possible that in future studies increasing or decreasing doping it may be possible to find the right ratio that favors their antibacterial effect.

In the case of nanoparticles of TiO_2:Fe (1.25%), there was not a significant decrease in optical density for *E. coli* and *S. aureus*, and p values greater than 0.05 obtained at the three concentrations used. As doping with Fe 1.25% decreases so does the antibacterial activity of nanoparticles of TiO_2. The null antibacterial activity by these nanoparticles could be related to the assimilation of Fe used in the metabolism of bacteria, since iron is an essential micronutrient for normal growth of most microorganisms. It should be mentioned that the bacteria have different mechanisms to capture environmental iron or a host. In Gram negative bacteria, the cell possesses outer membrane complex receptors that supply the energy required for iron transport (Ton complex) which allow the iron to pass through the outer membrane and is internalized into the cytoplasm via the cell membrane. In Gram positive bacteria, the iron binding to lipoproteins anchored in the cytoplasmic membrane, thus must traverse this membrane and peptidoglycan (Köster, 2001). Therefore doping with iron nanoparticles appears not to be a favorable option, at least when used as an antibacterial agent. But with this work forms a basis for assessing the antibacterial activity of nanoparticles with potential biomedical applications.

Conclusion

Nanoparticles of TiO_2 and TiO_2 (50% AcAc) have a higher activity against *E. coli* and *S. aureus*, and doping TiO_2 with Indium and Iron do not significantly enhance the antibacterial effect. At concentrations of 250 and 500 µg/ml the intrinsic nanoparticles significantly alter bacterial growth in the exponential phase and have a greater antibacterial effect on *E. coli* and *S. aureus*; TiO_2 (50% AcAc) nanoparticles have a greater bactericide effect.

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