Chapter 9

Biocompatibility of Doped Semiconductors Nanocrystals and Nanocomposites

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Abstract

Exposure of humans and environment to nanocrystals are inevitable, and nanotoxicological analyses are a requirement. The wide variety of nanocrystals with different applications is increasing, and characterization of their effects after exposure includes their potential toxicity and uses. This review summarizes the characterization of doped nanocrystals and nanocomposites, Ca-doped ZnO, Ag- and Eu-doped ZnO and Ni-doped ZnO NCs, their biocompatibility and applications. This review uncovers how these nanocrystals present desirable biocompatible properties, which can be useful as antitumoral and antimicrobial inducing agents, which differ markedly from toxic properties observed in other general nanocrystals.

Keywords: nanocrystals, nanocomposites, biocompatibility, doping, composites

1. Introduction

Cancer is one of the most common and serious diseases currently, considered a public health problem [1–3]. The prostate cancer, according to INCA, is the most accessible in men in Brazil and difficult diagnoses for slow development and absence of signaling in the early stages of the disease, and can progress to more advanced stages with metastasis. The success in treatment depend on the extent of cancer at the time of diagnosis and, thus, nanotechnology can be a tool to improve diagnostic technique and for improve the quality of treatments [4–10].

Breast cancer is considered as a heterogeneous disease in its pathological characteristics. The follow-up of the disease is quite complex, mainly due to the existence of the various tumor subtypes, which have different expression profile, therapeutic response and clinical behavior [4, 11–15]. The molecular classification divides breast cancers into many groups, based on molecular expression profile. Triple negative breast cancer (TNBC), characterized by lack of expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor type 2 (HER2), comprises the highest invasive potential and worst clinical outcome [16, 17]. In addition, this breast cancer presents survival rates significantly lower and recurrence rates significantly higher compared to other breast cancer subtypes [17–19]. Moreover, the identification of specific targeted therapy and improved diagnosis for TNBC is fundamental.

In the last decades, cancer has been presenting itself as a health problem public interest, raising the urgent interest in research for the development of drugs with antitumor activity. Nanotechnology has been a tool for development of new nanoparticles with antineoplastic properties [5, 20–23].

In recent years, with the emergence of certain biomedical problems, such as increased infections of pathogenic strains resistant to antimicrobials and the development of new cancers, the development of new effective tools has been extremely important. Therefore, the use of nanotechnology is important, since depending on the size and shape of nanocrystals it is possible to control their physical and chemical properties [24, 25].

The concern about pathogens and multi-drug microorganisms in food, veterinary and medical industry are boosting the demand for new antimicrobial substances. Since a large number of microorganisms have showed resistance against different antibiotics, the potential antimicrobial substance should be able to destroy or inhibit these microorganisms in different matrices and do not promote resistance [26–29]. Moreover, this compound should be cheap, easy to use, bacteria specific and non-toxicity to the human or animals.

Pathogenic microbial contamination and eradication of organic pollutants have been a major threat to mankind and the environment. Therefore, the development of new, more efficient materials with improved photocatalytic and antimicrobial activity is of great importance.

The increase in bacterial resistance towards conventional antibiotics generally occurs because some bacteria form slime which facilitates adhesion and formation of biofilms on any surface or implantable devices [30, 31]. Thus, the formation of biofilms increases bacterial resistance, preventing the action of antibiotics [32–36]. In order to reduce microbial adhesion, several researchers have been studying nanocrystals with antimicrobial properties as a promising tool to control microbial adhesion, since nanocrystals with catalytic properties have the potential to reduce biofilm formation [32, 35, 37–40].

Therefore, in the book chapter we investigated the cytotoxicity of Ag or Ca doped ZnO NCs in normal and tumor cells, as well as, the viability of ZnO doped with Ag, Eu, Ni and your nanocomposites against microorganisms.

2. Doped semiconductors nanocrystals and nanocomposites

The development of nanoparticles for medical purposes has been widely investigated, since when the size is greatly reduced at the nanometric scale, the reason surface/volume increase generating new and interesting properties, such as a greater ability to absorb drugs, probes and proteins [41] In addition to size and shape, a crystalline nanoparticle (NPs) alters as both physical and biological properties. For example, Spanó et al. have shown that amorphous nanoparticles are more genotoxic than crystalline (nanocrystals) [42]. In addition, a crystal phase in which nanocrystals (NCs) themselves also enables physical and biological properties [43].

The use of nanoparticles and nanocrystals as novel therapeutic antimicrobial agents have been described some of the metallic compounds possess antimicrobial property especially inorganic metal oxides [44]. Moreover, the alliance of nanotechnology and biology has brought to fore metals in the form of nanoparticles as potential antimicrobial agents.

Several types of nanocrystals have been synthesized in order to obtain an efficient nanomaterial. However, it is important to emphasize that nanocrystals must be biocompatible and specific [45]. Based on this and knowing that zinc oxide nanocrystals (ZnO) are biocompatible materials, according to the US Food and Drug Administration (FDA), in this chapter we investigated this nanocrystal.

Nanocrystals of zinc oxide (ZnO) exhibit many important characteristics, such as high catalytic activity, chemical and physical stability, as well as ultraviolet (UV) absorption [46, 47]. The technique most used to produce defects aiming to increase the catalytic activity in ZnO nanocrystals is based on the choice of synthesis methods [34], use of nanocomposite photocatalysts [48], and doping with impurities [49].

ZnO nanocrystals have the unique ability to induce oxidative stress in cancer cells and bacteria, being one of the main mechanisms of cytotoxicity and bactericidal action [32, 50, 51]. This property is due to the semiconductor nature of ZnO, which induces the generation of reactive oxygen species (ROS), leading to oxidative stress and cell death or bacteria [52–54]. Another type of nanocrystalline that enters the category of biocompatible is nickel because it is a basic element that is part of metalloproteins, being vital for living beings. Nickel (Ni), silver (Ag) and calcium (Ca) nanocrystals and oxide have several advantages as antimicrobial and antitumor agents [55–57].

Figure 1 shows the three-dimensional structures of the zinc, calcium, silver and nickel oxides, subsequently exemplifying the doping process and nanocomposites. The doping process consists of the substitution of ions in the crystalline structure of the nanocrystal. For example, in silver-doped ZnO nanocrystals, silver ions substitute the ions of Zn in the crystalline structure of ZnO.

The formation of nanocomposites is the mixing of two types of nanocrystals in order to potentiate a certain physical property, or the presence of two interesting physical properties.

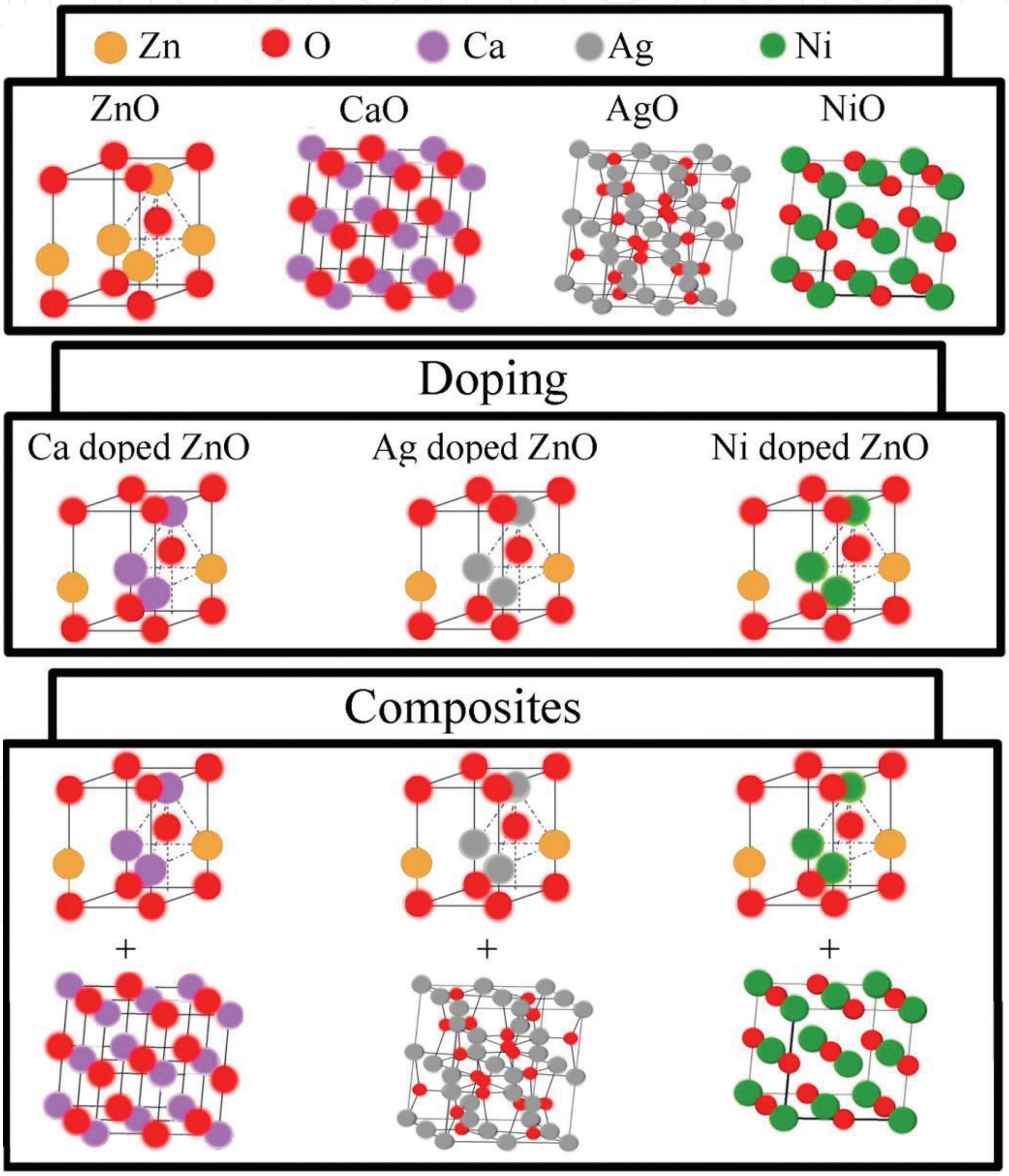

Figure 1. Three-dimensional structures of the zinc oxide, calcium oxide, silver oxide and nickel oxide, subsequently exemplifying the doping process and nanocomposites.

Chu et al. demonstrated that the mixture of titanium dioxide nanocrystals with silver oxide enhanced the photocatalytic performance [58]. Thus, as the photocatalytic performance of nanocrystals is directly related to antineoplastic effect and bactericidal action the study of the mixture of nanocrystals (nanocomposites) is extremely important.

2.1. Cytotoxicity of doped nanocrystals and nanocomposites in cells

Normal epithelial cell line (RWPE-1), prostate cancer cells (PC3) and human breast adenocarcinoma (MDA-MB-231), were cultured in RMPI medium supplemented with 10% fetal bovine serum (FBS) and 0.1% gentamycin. For the RWPE-1 strain, the medium was further enriched with epidermal growth factor (10 ng/mL) and bovine pituitary extract. Cells were maintained at 37°C, 5% CO_2. The cells were grown in 25 cm^2 bottles and transferred before reaching the confluence level (80%). Cell viability was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide (MTT) assay. Cells (1×10^5/well) were seeded in 96-well plates and incubated overnight for adherence. The culture medium was removed and replaced with medium containing the nanocrystals in different concentrations diluted in PBS and evaluated at 24 hours. After the indicated period, MTT (5 mg/mL) was added and the plates were incubated for 4 hours. Then, 50 μL of sodium dodecyl sulfate (SDS) (20%) was added in each well to dissolve the formazan crystal. The absorbance was measured at 570 nm. Next, the cell viability calculation was performed.

Figure 2 show the viability of nanocrystals in function of concentration for the (a) normal epithelial cell line (RWPE-1) and (b) prostate cancer cells (PC3) at 24 hours. In the RWPE-1 cells

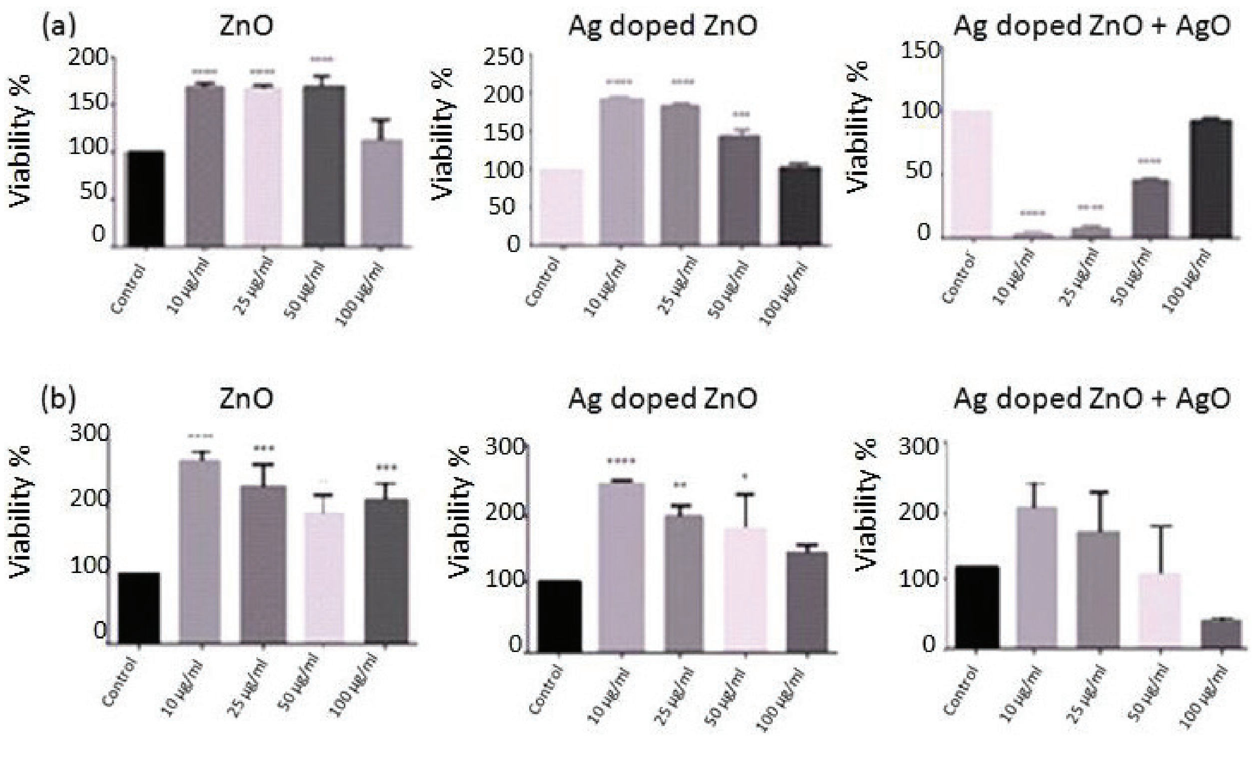

Figure 2. Viability of (a) RWPE and (b) PC3 after treatment with ZnO, Ag doped ZnO and nanocomposite (Ag doped ZnO and 68% of AgO NCs) with different concentration after 24 hours.

the ZnO NCs and Ag doped ZnO was not observed cytotoxic effect. However, in the composite formed by Ag doped ZnO and 68% of AgO NCs occurs the reduction in cell viability. For PC3 cells the ZnO and Ag doped ZnO NCs had no cytotoxic effect at all concentrations, but the composite had a significant inhibitory effect on cell viability, however, there was an increase in cell viability for PC3 cells at concentrations of 10 and 25 μg/mL in 24 hours time.

Figure 3 show the viability of Ca doped ZnO, ZnO and CaO nanocrystals in function of concentration for the human breast adenocarcinoma (MDA-MB-231) cells at 24 hours. The cytotoxic potential of CaO nanocrystals was extremely lower against cells and ZnO was performed significantly damage in cells. Interestingly, the Ca doped ZnO NCs displayed high cytotoxicity against the cells. The Ca doped ZnO NCs reduced the viability in a not dose-dependent manner, damaging about 40–93% of cells at concentrations of 12.5–100 μg/mL.

2.2. Cytotoxicity of doped nanocrystals and nanocomposites in bacteria

The ZnO doped with silver and europium has been tested in preliminary study against Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus* and *Enterococcus faecalis* using different methods. The agar well diffusion test was made according to Clinical and Laboratory Standards Institute and the resazurin microtiter assay plate testing was also performed.

The inhibition zone produced by ZnO doped with silver increase in Ag dopant concentration. The antimicrobial action proposed for nanocrystal against microorganisms can be related with: (a) the adherence of the nanomaterials on the surface of the bacteria, which can lead to physical blockage of transport channels of the cells; (b) the oxidation of membranes lipids by reactive oxygen species (ROS) like H_2O_2, singlet oxygen and hydroxyl radicals [44].

The viability assay against *S. aureus* and *E. coli* showed that the Ag and europium (Eu) doped ZnO NCs inhibited these microorganisms. However, the increase of Eu doping and Eu_2O_3 NCs promoted the growth of the microorganisms (**Figure 4**). Concentrations greater than 1% Eu occurs the formation of a nanocomposite that constitutes of Eu and Ag doped ZnO and EuO. The use of nanocrystals as antimicrobial substance should be promisor in different

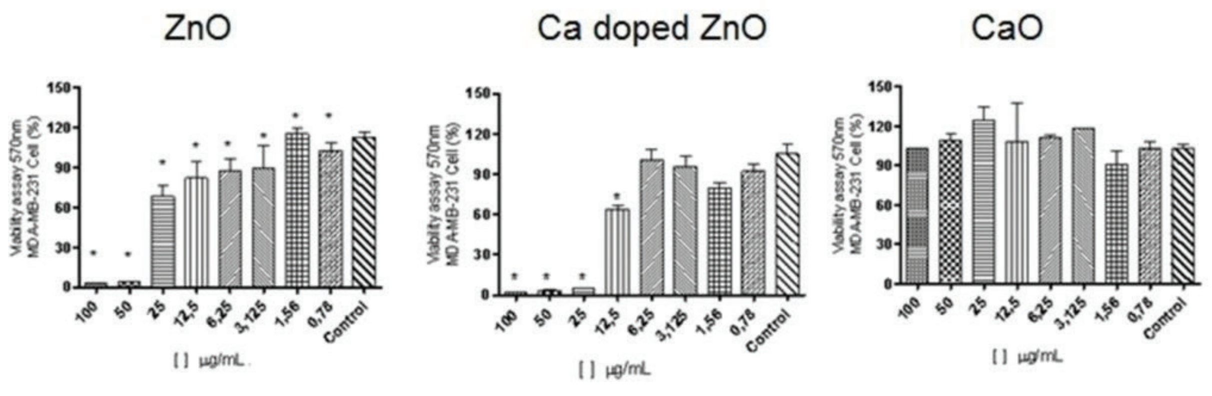

Figure 3. Viability after treatment with ZnO, Ca doped ZnO and CaO nanocrystals in function of concentration for the MDA-MB-231 cells at 24 hours.

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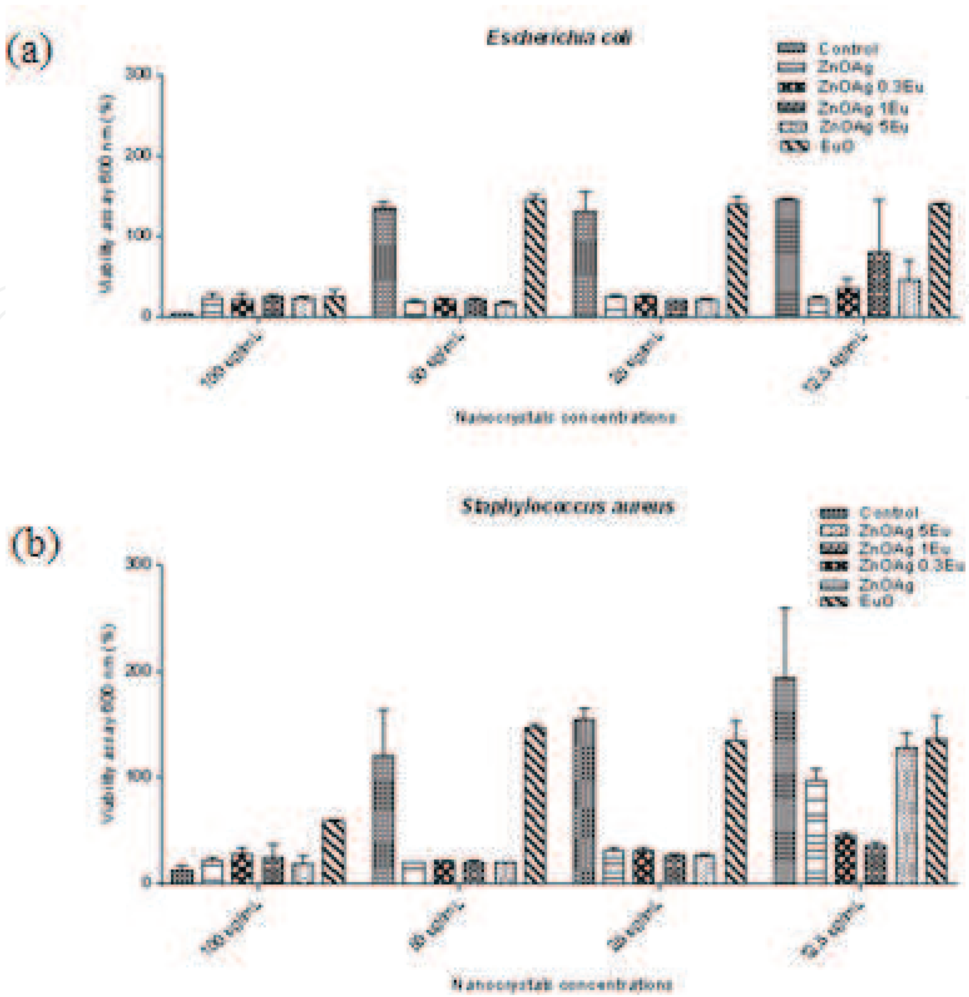

Figure 4. Viability assay against *S. aureus* and *E. coli* of Ag and Eu doped ZnO, and ZnO and EuO NCs.

areas. These NCs could be a potential antimicrobial, which can be apply in food, veterinary and medical industry. However, complementary studies should be done to better understand the effects of this compound on biological molecules.

The potential antimicrobial activity of nanocrystals against potential pathogens have been studied. On the other hand, large number of microorganisms have showed resistance against antibiotics [59, 60]. Zinc (Zn) and nickel (Ni) are transition metals that generate free electrons, so when these ions are incorporated into nanocrystals may amplify the bactericidal effect [61–64].

The viability assay against *Proteus vulgaris* and *Klebsiella pneumonia* with different concentration of the nanocomposite hybrid (Ni doped ZnO + NiO NCs), ZnO and NiO NCs (**Figure 5**). Observed that NiO NCs showed antimicrobial activity against all microorganisms tested. *P. vulgaris* was the most sensitive in presence of NiO NCs, whereas *K. pneumonia* was more resistant. The antimicrobial effect may be due to production of electron–hole pairs. After a cascade of reactions, hydrogen peroxide is produced and penetrate into the cell, destroy the membrane, denatures proteins and damages DNA causing cell death [31, 38, 51]. Therefore, due to its simple preparation, low cost and antibacterial activity, these NCs have potential to be used as antibacterial agents against a wide range of microorganisms.

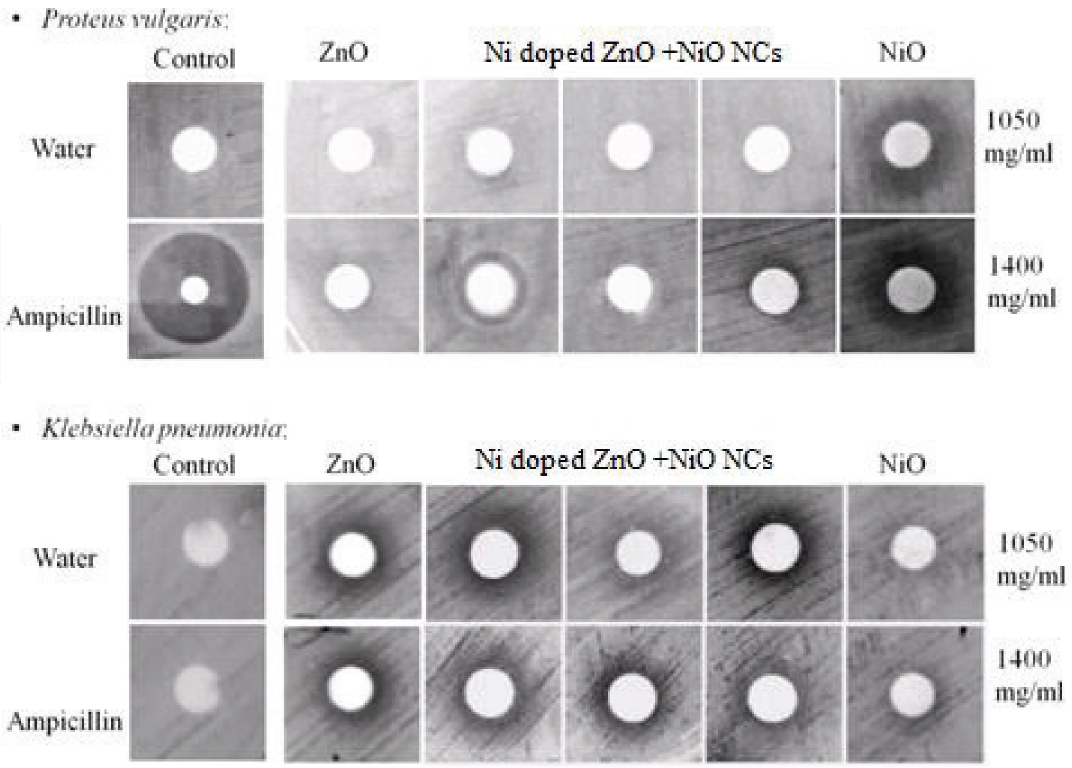

Figure 5. Viability assay against *Proteus vulgaris* and *Klebsiella* pneumonia with different concentration of the nanocomposite hybrid with ZnO, Ni doped ZnO + NiO and NiO NCs.

3. Conclusion

The cytotoxicity analysis of Ag or Ca doped ZnO NCs in normal, tumor prostate and breast cells was possible to identify the antitumor effect potentialization when these ions (Ag and Ca) were incorporated into ZnO NCs. In this way, these doped NCs can become a target in the treatment of cancer. The viability assay against microorganisms showed that the increase of Eu doping in ZnO NCs promoted the growth of the microorganisms and Ni doped ZnO with NiO NCs are more efficient than NiO NCs to *K. pneumonia.*

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Conflict of interest

The authors have no conflicts of interest.

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