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RESEARCH PAPER

A Dual-Function Approach for Cancer Therapy and Environmental Remediation with Advanced Photocatalytic, Antibacterial, and Antioxidant Properties: Gold-Doped Zinc Oxide Nanoparticles

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ABSTRACT

In recent years, the removal of industrial wastewater has emerged as a significant environmental challenge. In this study, we aimed to introduce a nanoparticle with not only catalytic removal properties but also biological capabilities in anticancer, antibacterial, and antioxidant applications. Gold-doped zinc oxide nanoparticles were synthesized in the presence of *sambucus nigra* extract. The synthesized nanoparticles were characterized using SEM, EDS, TEM, FT-IR, and XRD. The results revealed that the nanoparticles exhibited high purity and a spherical morphology. The photocatalytic degradation of methyl orange by the ZnO-Au nanoparticles demonstrated their high degradation efficiency under both UV and visible light conditions. Anticancer activity assays indicated that the ZnO-Au nanoparticles showed significant effectiveness against AGS and MCF-7 cancer cell lines. Furthermore, the ZnO-Au nanoparticles exhibited strong antibacterial activity against both Gram-positive and Gram-negative bacteria, with a more pronounced effect observed against Gram-negative bacteria. Additionally, the antioxidant activity of the synthesized nanoparticles showed an increase in DPPH inhibition percentage with higher nanoparticle doses. Overall, our results suggest that the synthesized nanoparticles possess unique capabilities in both environmental and biological applications.

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INTRODUCTION

Nanoscience, as a fascinating and powerful field of study, offers a wide range of innovative, reasonably priced results, and applications. Due to the quantum size effect, nanoparticles (NPs) with sizes between 1 and 100 nm have remarkable magnetic, electrical, and optical characteristics. Research on nanotechnology is currently

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having a greater impact on the food processing, pharmaceutical, environment, energy, and farming industries [1].

These days, scientists are interested in creating different hybrid metal oxide nanomaterials because of their special uses in almost every field. Additionally, the most recent innovations in nanotechnology that have developed ZnO in nanostructured forms, such as nanowires, nanoparticles, nanolayers, and nanocomposites, expand the range of potential applications. Zinc Oxide (ZnO) nanoparticles are among the transition metal oxides that are used in a variety of applications, including chemical sensors, cancer treatment, DNA detection, photocatalysts, ceramics, antibacterial, anti-UV additives, and photoelectric fields [2-4].

The synthesis conditions of ZnO NPs determine their shape, which can take on a wide range of morphologies [5]. Each morphology has its own unique set of physicochemical properties, which are influenced by the specific synthesis mechanism used. By controlling the synthesis conditions, researchers can design ZnO NP structures with optimal antibacterial activity [6]. The surface activity of ZnO NPs is a key factor in determining their morphology, which is influenced by the surface conditions. The proportion of active surface sites on the nanoparticles was used to investigate the shape-dependent activity of ZnO NPs.

Different synthesis methods and growth conditions can produce nanoparticles with diverse active surfaces, leading to varying antibacterial activities [7, 8]. ZnO NPs have been shown to disrupt the structural integrity of bacterial cells by direct contact with cell walls, while also releasing antimicrobial ions, particularly zinc ions, and reactive oxygen species (ROS). The morphology of ZnO NPs has been found to play a significant role in determining their antibacterial activity, which is crucial for ensuring food safety and health [9]. The antibacterial mechanisms of ZnO NPs have been proposed to include: I. the production of reactive oxygen species (ROS) through photocatalytic activity, II. the induction of oxidative stress in bacterial cells, III. the physical attachment of ZnO NPs to bacterial cell walls, IV. the release of zinc ions (Zn(II)), and V. genotoxic effects on bacterial DNA [10].

ZnO NPs have been investigated as a potential biocompatible and biodegradable nanoplatform for cancer treatment. This is due to their ability to generate ROS upon contact with cancer cells, which can cause mitochondrial damage and activate cell death [11, 12]. The electrostatic properties of ZnO NPs facilitate their rapid uptake by immune cells, providing a potential platform for combination therapy with immunotherapy in cancer treatment [13]. Moreover, the versatility of ZnO NPs allows for the loading of different types of drugs, including doxorubicin, paclitaxel, curcumin, and baicalin, as well as DNA fragments, which can improve their solubility, efficacy, and targeted delivery to cancer cells [14]. Mongy et al. synthesized ZnO NPs using *Rhus coriaria* extract, which exhibited anticancer activity against breast cancer cells by inducing apoptosis, arresting cell cycle at S-phase, and inhibiting colony formation and metastasis. The study also found that the nanoparticles modulated genes involved in apoptosis and metastasis [15].

On the other hand, there has been a lot of interest in gold nanoparticles (AuNPs) because of their distinct physicochemical characteristics, which differ greatly from bulk gold's. The amazing optical features of gold nanoparticles, such as high light absorption and scattering, are attributed to their unique surface plasmon resonance (SPR). In addition, they are exceptional biological agents with superior antimicrobial, antibacterial, and genotoxic qualities, as well as the ability to carry drugs and genes. Gold nanoparticles are employed in biological imaging, radiotherapy, tumor imaging, biological imaging, and diagnostic assays. Colloidal gold has been used to treat autoimmune diseases, especially those affecting the bone joints, which have shown pain relief [16].

The utilization of natural products in the chelation, reduction, or precipitation of a metal ion precursor has attracted attention in comparison to traditional chemical and physical synthetic approaches [17]. This process involves use of safe, nontoxic, biosafe, and environmentally friendly products. The use of biological components and natural extracts from plant parts (leaves, roots, flowers, and fruits), as well as biometabolites from organisms like bacteria, algae, fungi, etc., are examples of environmentally friendly approaches for synthesizing nanoparticles (NP) [18]. The main aim of this study was to create a new technique for producing ZnO and gold nanoparticles from *sambucus nigra* extract and then assess their oxidant, antibacterial, anticancer, and

photocatalytic characteristics.

MATERIALS AND METHODS

Methods

To synthesize gold-doped zinc oxide nanoparticles, gold salt ($HAuCl_4 \cdot 3H_2O$), rhodamine B ($C_{28}H_{31}ClN_2O_3$) dye, zinc salts ($Zn(NO_3).6H_2O$), polyvinylpyrrolidone (PVP), methanol (CH_3OH), and ethanol (C_2H_6O), all procured from Sigma-Aldrich, were utilized. Double-distilled water was employed in the synthesis of nanoparticles as well as in the evaluation of their biological and photocatalytic activities. Various strains of Gram-positive and Gram-negative bacteria were purchased from Pasteur Institute of Iran.

Preparation of sambucus nigra extract

The preparation of the red *sambucus nigra* extract was carried out in several stages: I) The *sambucus nigra* plant was collected from the forests of Mazandaran Province, Iran. II) The plant was dried at room temperature and subsequently ground into a powder. III) 25 g of the powdered plant were immersed in 100 ml of methanol in a separatory funnel for 3 days. IV) The solvent was removed using a rotary evaporator, yielding the *sambucus nigra* extract.

Green synthesis ofZnO and ZnO/Au nanoparticles

The synthesis of gold-doped zinc oxide nanoparticles involves two main stages: I) synthesis of zinc oxide nanoparticles, and II) doping of these nanoparticles with gold. Firstly, 0.7 g of zinc nitrate was dissolved in 20 ml of distilled water. In a separate container, 1 g of polyvinylpyrrolidone (PVP) was dissolved in 20 ml of distilled water and gradually added to the reaction vessel. The reaction continued under vigorous stirring. The pH of the solution was adjusted to 12 by the addition of 1 M sodium hydroxide. After 2 h, the resulting milky precipitate was centrifuged and washed three times. The obtained powder was then calcined at 550°C for 3 h. For the synthesis of gold-doped zinc oxide nanoparticles, 0.5 g of the zinc oxide powder synthesized in the previous step were dispersed in 20 ml of distilled water. Subsequently, 48 mg of gold salt, dissolved in 3 ml of distilled water, was carefully added to the reaction vessel. Finally, 2 ml of *sambucus nigra* extract were added dropwise to the reaction mixture under gentle stirring. After 2 h, the formed precipitate was washed three times with water and ethanol and dried at room temperature for 48 h.

Antibacterial activity

Antimicrobial activity was determined by using the broth microdilution method [19]. *sambucus nigra* extract, ZnO NPs, and gold-doped ZnO nanoparticles were investigated for their antibacterial efficacy against four bacterial strains including Gram positive and negative bacteria (*Escherichia coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 9997), *Staphylococcus aureus* (ATCC 29213), and *Enterococcus faecalis* (ATCC 29212). The MIC (the minimum inhibitory concentration) was considered the lowest concentration of the material at which no turbidity was observed in the wells. The MBC (the minimum bactericidal concentration) was the lowest concentration of samples that showed 99.9% bacterial mortality and inhibited the growth of bacterial colonies.

Anticancer activity

The cytotoxic effects of gold-doped ZnO nanoparticles were investigated in a recent study using the MTT method, which focused on the nanoparticles' influence on mitochondrial function. MCF-7 (human breast cancer) and AGS (human gastric adenocarcinoma) cell lines were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with penicillin (100 units/ml), streptomycin (100 µg/ml), fetal bovine serum (10%), and maintained at 37°C with 5% CO_2. Following a 24 h incubation period, cells were seeded in 96-well plates at a density of 110^4 cells per well. The culture medium was replaced with a fresh medium containing different concentrations of nanoparticles (6.25, 12.5, 25, 50, 100, 200, and 400 µg/ml), and incubated for an additional 24 h. The cells underwent a series of steps involving an initial incubation with MTT (0.5 mg/ml) for 4 h, followed by the addition of DMSO (100 µl), and finally, the absorbance was measured at a wavelength of 570 nm. To determine the cell survival percentage for each treatment, the measured optical density (OD) was compared to the control, and this comparison was performed in triplicate for each concentration group.

Photocatalytic activity

To evaluate the photocatalytic activity of ZnO NPs and gold-doped ZnO nanoparticles using methyl orange (MO), a MO solution (10 ppm) was

prepared, and nanocatalyst (0.6 g/l) were dispersed in it. After 30 min of darkness to reach adsorption equilibrium, the mixture was continuously stirred and subjected to UV and visible light. To measure the degradation of MO, samples were obtained on a regular basis, filtered, and tested using UV-Vis spectrophotometry. Control experiments without nanocatalyst was conducted to ensure an accurate assessment of photocatalytic activity.

Antioxidant activity

We evaluated the nanoparticles' antioxidant activity by calculating the percentage of 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical inhibition [20]. In detail, the microwells were first filled with 10 µl of sample and then filled

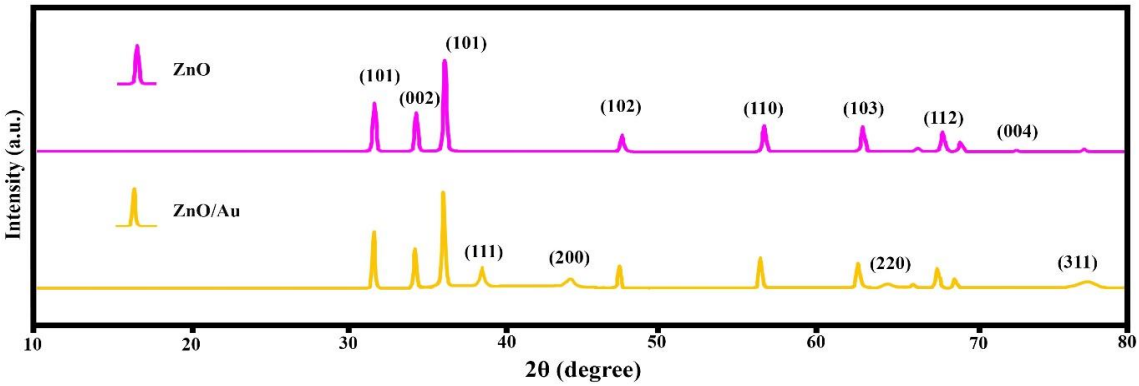

Fig. 1. XRD spectrum of ZnO and gold-doped ZnO nanoparticles.

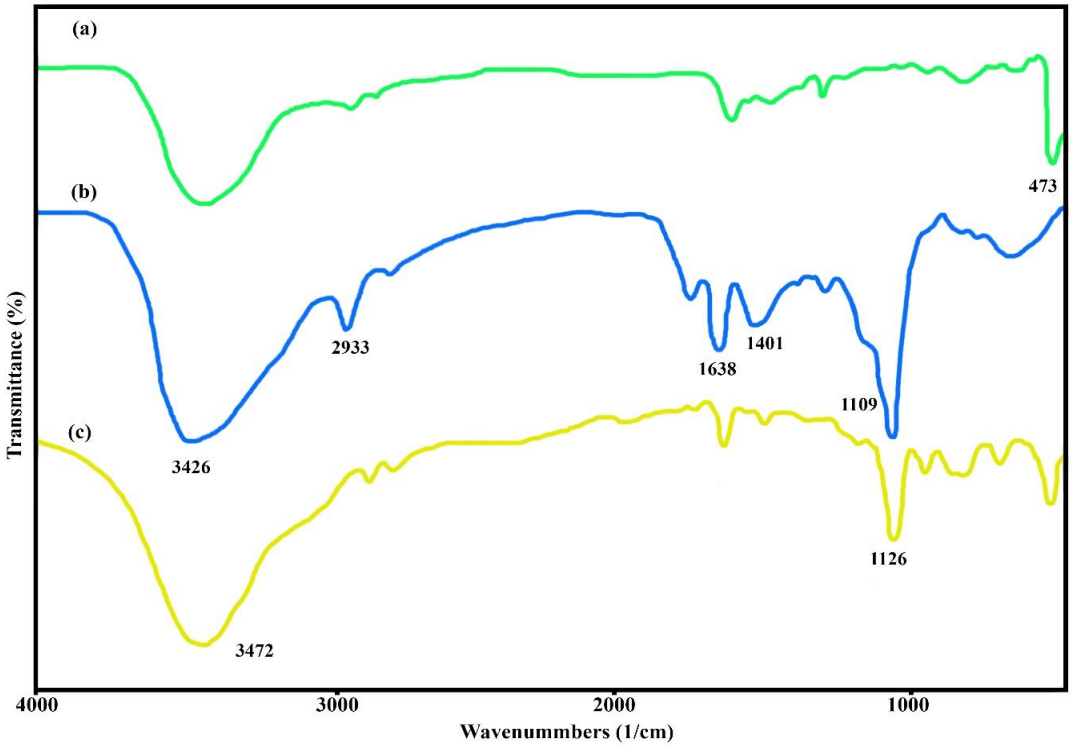

Fig. 2. FTIR spectrum of (a) ZnO, (b) *sambucus nigra* extract, and (c) gold-doped ZnO nanoparticles.

with 250 µl of DPPH solution. For thirty seconds, the resulting mixture was mixed. When exposed to hydrogen donors, the purple color of DPPH radicals in the organic solvent fades and changes to yellow, signifying the test substance's decrease of DPPH radicals. After incubating for 20 min at room temperature, absorbance was taken at 517 nm. Higher antioxidant activity of the sample is correlated with a more notable reduction in color intensity. The percentage of DPPH radical inhibition was calculated and recorded in the findings.

$$\text{Reduction } (\%) = (A_0 - A_t) / A_0 \times 100$$

where A_0 is the absorbance of the control (DPPH solution without antioxidant) and A_t is the absorbance of the test sample (DPPH solution with antioxidant).

RESULTS AND DISCUSSION

XRD

The X-ray diffraction (XRD) spectrum of ZnO nanoparticles is shown in Fig. 1. The spectrum observed in this study was fully consistent with the standard diffraction pattern of ZnO and exhibited a hexagonal crystal structure related to wurtzite (Joint Committee on Powder Diffraction Standards, JCPDS, No. 01-080-0075). The synthesized ZnO nanoparticles had absorption peaks at 2θ angles of 31.1, 34.6, 36.4, 47.3, 56.7, 62.9, 67.4, and 72.2. According to JCPDS No. 01-080-0075, these observed peaks corresponded to the (100), (002), (101), (102), (110), (103), (112), and (004) Miller planes, respectively. Zaimbashi et al. also synthesized ZnO nanoparticles, and their XRD spectra showed similar results to the present study [21]. The XRD spectrum of ZnO-Au nanoparticles, shown in Fig. 1, revealed peaks like those observed in the XRD spectrum of ZnO nanoparticles, though with lower intensity, likely due to the presence of gold nanoparticles on ZnO nanoparticles. Additionally, four extra peaks at 2θ angles of 38.06, 44.41, 64.53, and 77.16 degrees were noted, corresponding to the standard diffraction of gold (JCPDS, No. 00-004-0784) and the (111), (200), (220), and (311) planes of

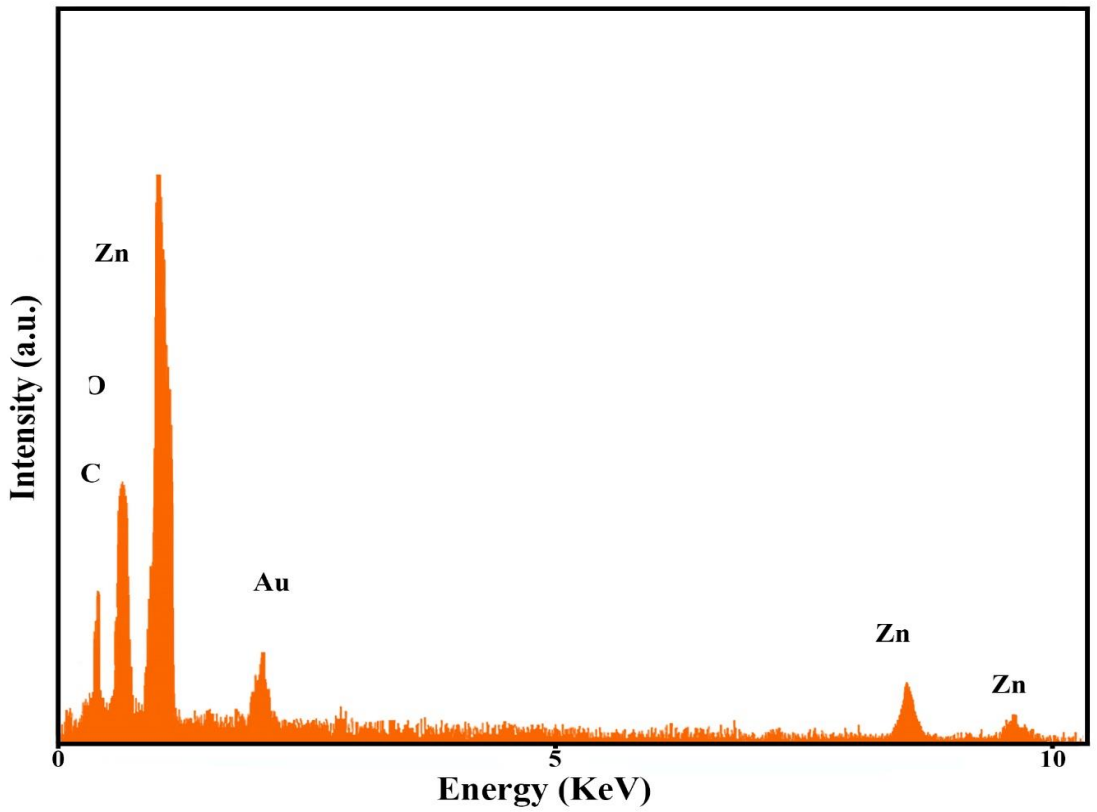

Fig. 3. EDS spectra of gold-doped ZnO nanoparticles.

cubic gold. Yang et al.'s study also showed these additional peaks related to gold nanoparticles after integrating gold nanoparticles into the structure of ZnO nanoparticles [22]. No additional peaks were visible in the XRD spectrum of ZnO and gold-doped ZnO nanoparticles, indicating the high purity of the synthesized nanoparticles.

FTIR

In this study, Fourier-transform infrared spectroscopy (FTIR) analysis was performed to investigate the functional groups present in ZnO, gold-doped ZnO nanoparticles, and the *sambucus nigra* extract. The stretching of the Zn-O bond is visible in the FTIR spectrum in the range of 400-600 cm^{-1} [23]. As shown in Fig. 2a, the synthesized ZnO nanoparticles had absorption at 473 cm^{-1}, confirming the formation of Zn-O bonds. In the FTIR spectrum of the *sambucus nigra* extract (Fig. 2b), a broad peak at 3426 cm^{-1} was observed, related to the O-H group present in water molecules and phenolic compounds. The peak at 2933 cm^{-1} corresponded to C-H aliphatic groups, and the peak at 1638 cm^{-1} was related to C=O bond in the aromatic rings of phenolic compounds [24]. The peak observed in the 1109 cm^{-1} corresponds to the C-O stretching bond. The presence of the C-O-H bond in the plant extract was confirmed by the 1401 cm^{-1} peak [25]. The FTIR spectrum of gold-doped ZnO nanoparticles showed absorption peaks similar to those of the plant extract and ZnO nanoparticles. The similarity of absorption peaks in gold-doped ZnO nanoparticles with those of extract nanoparticles confirmed the presence of extract on the surface of ZnO-Au nanoparticles. The similarity with peaks in the plant extract's FTIR spectrum confirmed the presence of the plant extract around ZnO-Au nanoparticles [26].

EDS, SEM and TEM

Energy-dispersive X-ray spectroscopy (EDS) analysis was employed to investigate the elemental composition of the nanoparticles. As shown in Fig. 3, the presence of carbon (at 0.4 KeV), gold (at 2.2 KeV), oxygen (at 0.5 KeV), and zinc (at 1 KeV) elements indicate the formation of nanoparticles with high purity. The detection of carbon is attributed to the red beetroot extract, confirming that the extract has been successfully incorporated onto the synthesized

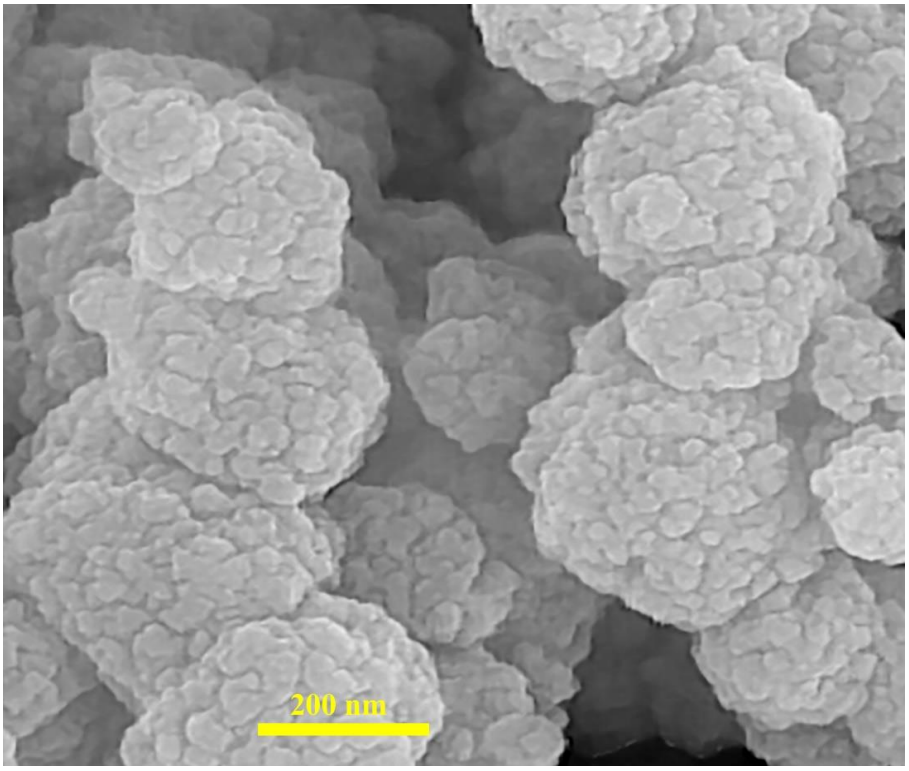

Fig. 4. SEM image of gold-doped ZnO nanoparticles.

nanoparticles. The scanning electron microscopy (SEM) images of gold-doped ZnO nanoparticles is shown in Fig. 3. As observed, the morphology of the particles is not clearly defined due to the presence of the extract. To obtain precise particle size measurements, TEM analysis is required. However, spherical morphology can be discerned in some regions. Transmission electron microscopy (TEM) images provide detailed information about the morphology and size of nanoparticles. TEM images of ZnO-Au nanoparticles (Fig. 5) showed spherical morphology and sizes of about 55-75 nm. Gold nanoparticles appeared as dark spots on ZnO nanoparticles in Fig. 5. The gold nanoparticles doped on ZnO nanoparticles had a spherical morphology. The plant extract around gold-doped ZnO nanoparticles appeared as dark shadows around ZnO-Au nanoparticles [27].

Antibacterial activity

Table 1 shows the results of examining the antibacterial properties of ZnO, gold-doped ZnO

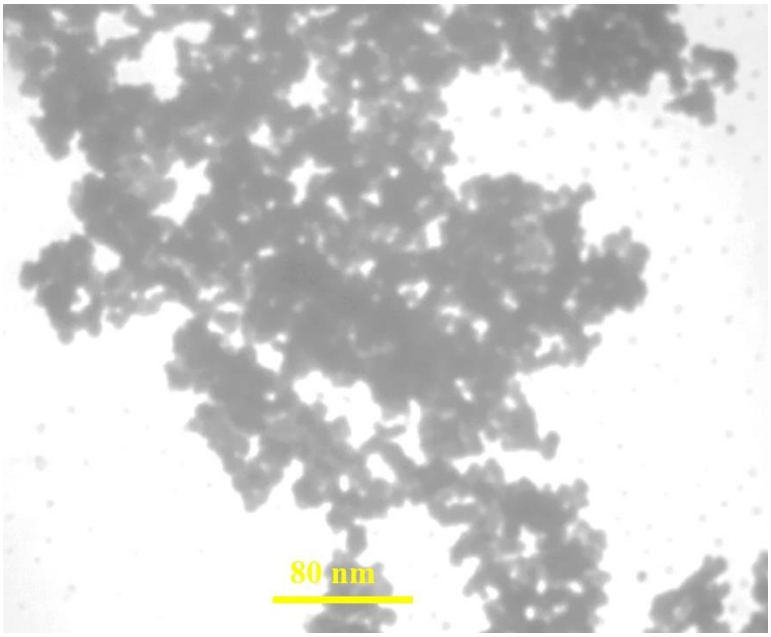

Fig. 5. TEM images of gold-doped ZnO nanoparticles.

Table 1. Antibacterial activity of ZnO, *sambucus nigra* extract, and gold-doped ZnO nanoparticles against Gram-positive and Gram-negative strains.

Strains	*sambucus nigra*		ZnO NPs		ZnO/Au NPs	
	MIC (mg/ml)	MIC (mg/ml)	MIC (µg/ml)	MBC (µg/ml)	MIC (µg/ml)	MBC (µg/ml)
E. faecalis	5	>5	500	500	1000	2000
S. aureus	>5	>5	500	1000	500	1000
K. pneumoniae	>5	>5	250	500	500	1000
E. coli	>5	>5	250	500	125	1000

nanoparticles, and *sambucus nigra* extract. Among the various compounds tested, the plant extract had the least antibacterial properties, showing its greatest effect on the *Escherichia coli* bacterial strain with an MIC of 5 mg/ml. It had no effect on *Enterococcus faecalis*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* bacterial strains. Both ZnO and gold-doped ZnO nanoparticles exhibited antibacterial properties on all tested strains, but ZnO nanoparticles had less antibacterial effect than ZnO-Au nanoparticles. ZnO and gold-doped ZnO nanoparticles inhibited the growth at concentrations of 250 and 125 µg/ml against *Escherichia coli* and 250 and 500 µg/ml against *Klebsiella pneumoniae*, 500 and 1000 µg/ml against *Enterococcus faecalis,* and 500 and 500 µg/ml against *Staphylococcus aureus* bacteria, respectively. Dediu et al. also demonstrated that the addition of gold nanoparticles to ZnO nanoparticles enhances antibacterial properties, consistent with the results of this study [28]. Gold-doped ZnO nanoparticles exhibited greater antibacterial effects on Gram-negative bacterial strains compared to Gram-positive strains. This difference is related to the structure and composition of the cell walls of these two types of bacteria. Gram-positive bacteria have a thick peptidoglycan wall, while Gram-negative bacteria have a thin wall that facilitates penetration and damage by nanoparticles [29]. The proposed mechanism of antibacterial activity of the nanoparticles against bacteria is summarized in Fig. 2.

Antioxidant activity

Free radicals are highly reactive molecules that damage body cells by reacting with cellular components, potentially causing diseases such as cancer, cardiovascular diseases, and autoimmune disorders [30]. Antioxidant systems in the cell neutralize these free radicals. If the amount of free radicals exceeds the cell's neutralization capacity, these radicals can damage cellular components and cause diseases. Substances with antioxidant properties reduce free radicals, minimizing damage [31]. As shown in Fig. 7a, the *sambucus nigra* extract exhibited 76% inhibition of the DPPH free radical at the highest tested concentration of 25 mg/ml. ZnO nanoparticles at the concentration of 1 mg/ml inhibited 48% of the DPPH free radical (Fig. 7b). Gold-doped ZnO nanoparticles revealed the highest antioxidant properties (Fig. 7c). With increasing concentration, the percentage of DPPH free radical inhibition also increased, with ZnO-Au nanoparticles inhibiting 22% of DPPH free radicals at 62.5 µg/ml and 86% at 500 µg/ml.

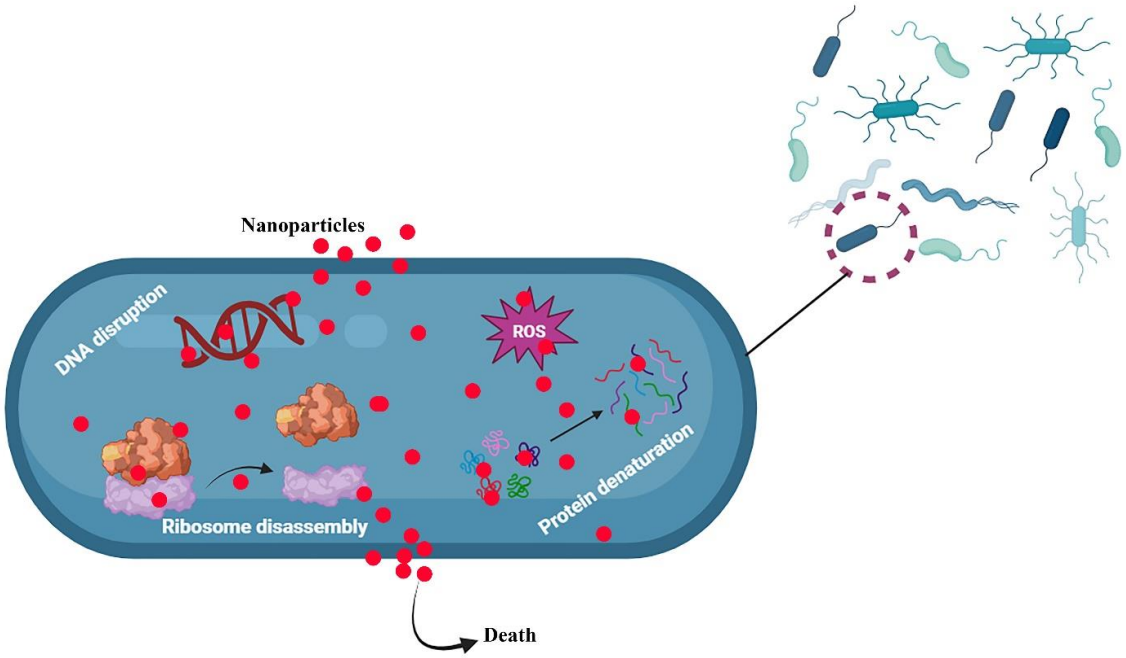

Fig. 6. Proposed mechanism of antibacterial performance of gold-doped ZnO nanoparticles.

The enhanced antioxidant property of ZnO-Au nanoparticles is related to the synergistic effects of gold nanoparticles inherent antioxidant property and the plant extract [32].*Anticancer activity*

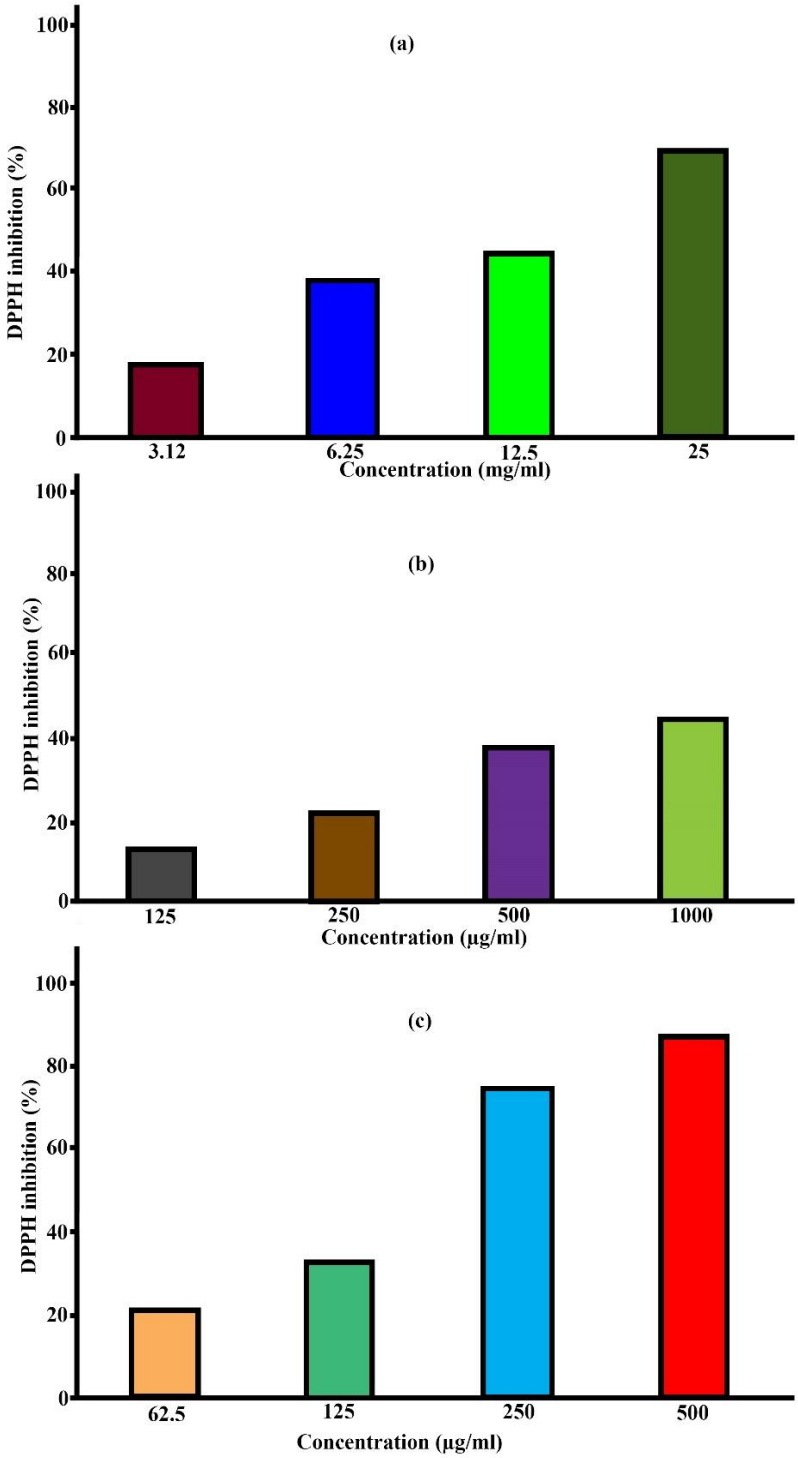

Fig. 7. Antioxidant activity (DPPH free radical) of (a) *sambucus nigra* extract, (b) ZnO, and (c) gold-doped ZnO nanoparticles.

Nanoparticles are increasingly recognized as potential treatments for various diseases, including cancer. They can function as anticancer agents or carriers of anticancer drugs, enabling targeted treatment and reducing drug side effects [33]. Fig. 8 illustrates the anticancer properties of gold-doped ZnO nanoparticles. In this study, the anticancer effects were evaluated on gastric cancer (AGS) and breast cancer (MCF-7) cell lines. The results indicated that gold-doped ZnO nanoparticles exhibited anticancer properties in a concentration-dependent manner. Specifically, the IC50 values for ZnO-Au nanoparticles were 76.1 µg/ml for MCF-7 and 29.7 µg/ml for AGS cell lines. Studies on ZnO and gold nanoparticles reveal their substantial potential in destroying cancer cells [34, 35]. Research on doped ZnO nanoparticles also shows that doping can significantly enhance their anticancer properties [36]. The combination of different nanoparticles creates synergistic effects, increasing their anticancer efficacy. Metal nanoparticles can induce apoptosis and elevate oxidative stress in cancer cells, leading to their destruction [37, 38].

Photocatalyst activity

The discharge of dyes from textile industries is a major environmental issue. Removing these

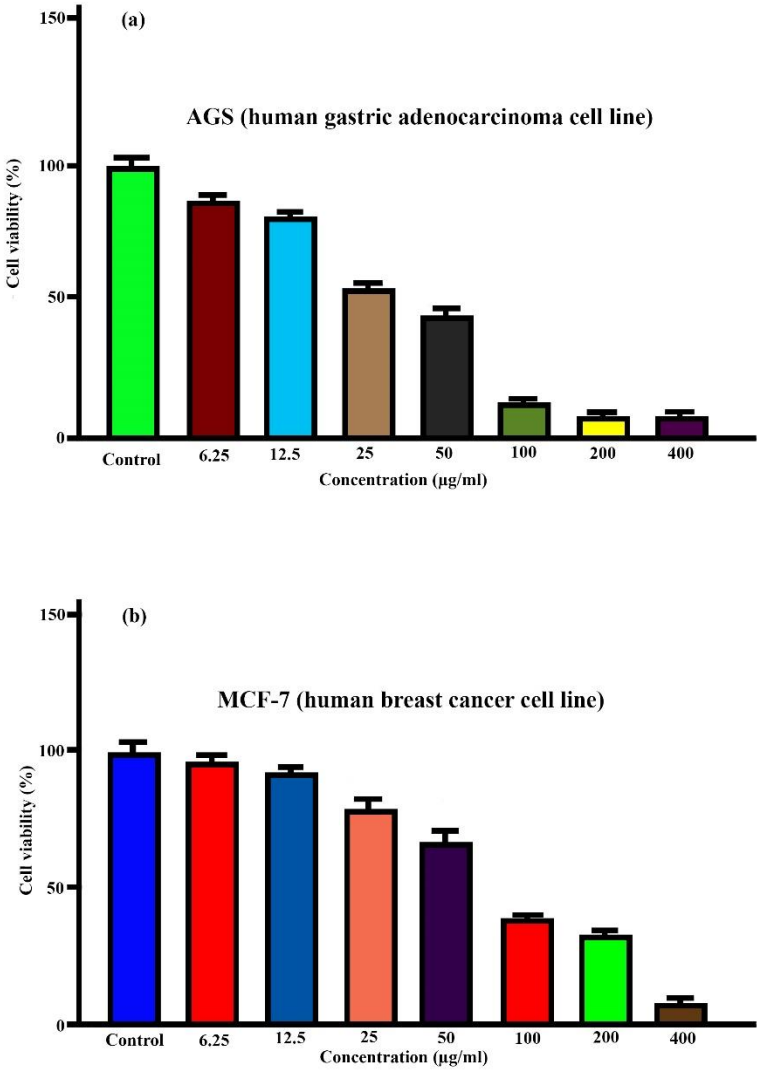

Fig. 8. Anticancer activity of gold-doped ZnO nanoparticles on (a) AGS and (b) MCF-7 cancer cell lines.

dyes from wastewater is both challenging and costly, and their presence in the environment poses significant problems. Methyl orange dye, widely used in the textile industry, is difficult to

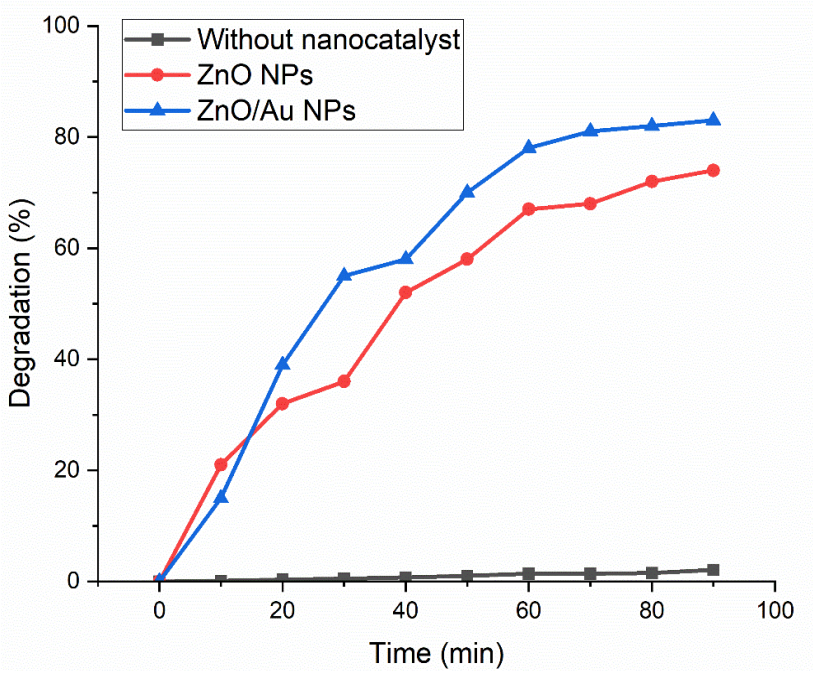

Fig. 9. Degradation of MO by ZnO and gold-doped ZnO nanoparticles under UV light condition.

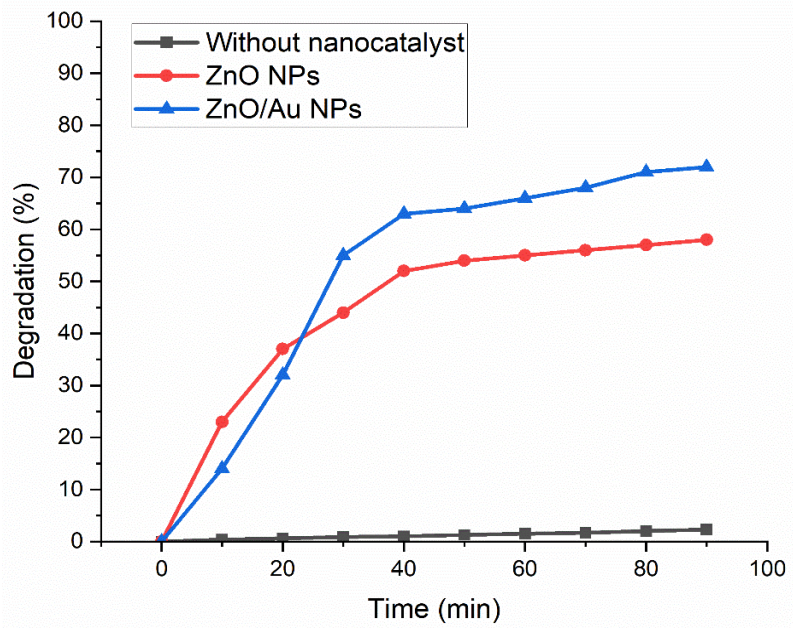

Fig. 10. Degradation of MO by ZnO and gold-doped ZnO nanoparticles under visible light condition.

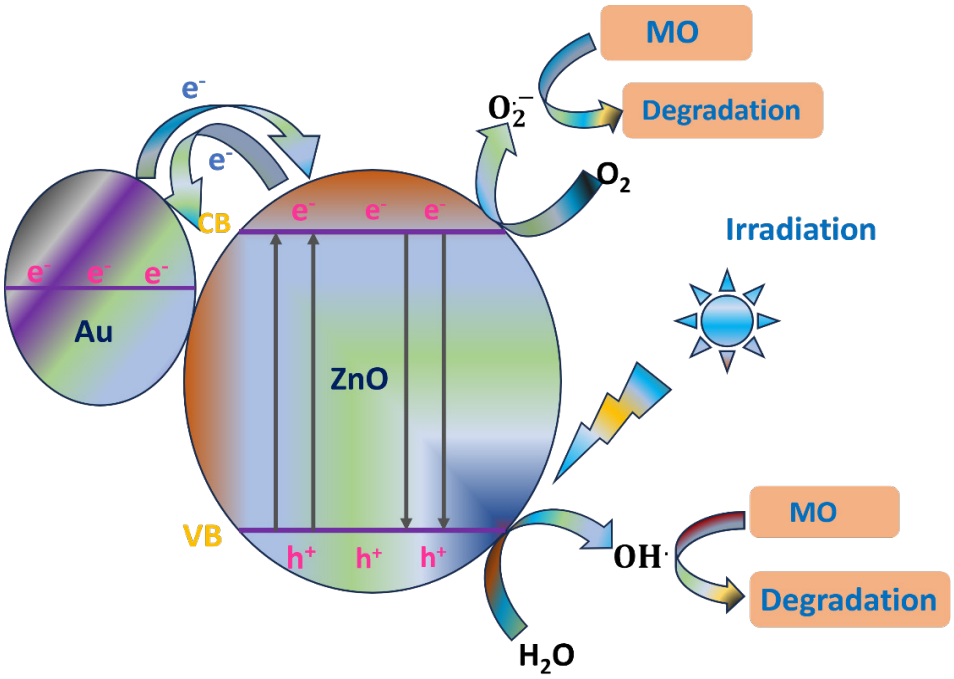

Fig. 11. Schematic mechanism for the methyl orange degradation.

remove due to its cyclic structure [39]. This study examined the degradation of methyl orange dye under visible and ultraviolet light using ZnO and gold-doped ZnO nanoparticles. As shown in Fig. 9 and Fig. 10, ZnO nanoparticles achieved a 59.8% degradation of methyl orange under visible light and 69.2% under ultraviolet light within 90 min. gold-doped ZnO nanoparticles, under the same conditions, resulted in a 73.1% degradation under visible light and a 87.2% degradation under ultraviolet light. This study aligns with Haspulat et al.'s findings, which show that ultraviolet light leads to more significant color degradation compared to visible light [40]. Various studies indicate that incorporating a metal with ZnO nanoparticles reduces the band gap and significantly enhances their photocatalytic properties [41]. Ahmad et al. observed that gold nanoparticles combined with ZnO nanoparticles improve photocatalytic activity due to reduced electron-hole recombination [42]. The primary photocatalytic reaction involves the destruction of substances through free radicals [43]. When nanoparticles are exposed to light, they absorb energy, causing electrons in the valence band to move to the conduction band [44]. These electrons can transfer to surrounding molecules, such as oxygen, forming superoxide radicals. Additionally, the creation of holes in the valence band attracts electrons from surrounding molecules like hydroxyl, generating hydroxyl radicals. These highly reactive radicals contribute to the degradation of pollutants, including methyl orange dye [45, 46]. The proposed mechanism of the photocatalytic process is illustrated in Fig. 10.

CONCLUSION

This study demonstrates the successful synthesis of gold-doped ZnO nanoparticles with remarkable multifunctional properties. The high purity and spherical morphology of the nanoparticles, coupled with their effective photocatalytic activity under UV and visible light, highlight their potential for environmental remediation. Additionally, their significant anticancer and strong antibacterial activities, particularly against Gram-negative bacteria, underscore their versatility in biological applications. The observed antioxidant properties further enhance their applicability. Overall, the gold-doped ZnO nanoparticles exhibit unique and promising attributes that can contribute to advancements in both environmental and biomedical fields.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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