



Preparation and antibacterial properties of gold nanoparticles: a review

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Abstract

The overuse of antibiotics has led to an increase in bacterial resistance and, in turn, to a decreasing efficiency of the rare available antibiotics. Alternatively, gold nanoparticles are promising antibacterials due to their high specific surface area, easy modification by functional groups and broad-spectrum antibacterial activity. Their antibacterial properties are closely related to particle size, dispersibility and surface modification, which can be tuned by adjusting reaction conditions. Here, we review the synthesis and antibacterial performance of gold nanoparticles in the raw form or modified with metal, organic compounds and carbon. We present the effect of reaction conditions on particle dispersibility and size. We compare the various synthesis methods. Antibacterial activities and their mechanisms are discussed.

Keywords Gold · Nanoscale materials · Functionalization · Preparations · Antibacterial activity · Mechanisms

Abbreviations

AuNPs	Nanoscale gold particles
g-C ₃ N ₄	Graphitic carbon nitride
MDR	Multi-drug resistant
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant <i>S. aureus</i>
ROS	Reactive oxygen species

Introduction

Abuse of antibiotics has become a growing problem in recent years. When antibiotics enter the environment, they damage the ecosystem's bacteria, aquatic organisms, soil organisms and plants. Of particular concern, bacteria eventually develop resistance or even multi-drug-resistant (MDR) "super bacteria." They can produce inactivating enzymes

and block drugs by altering cytomembrane permeability (Hu et al. 2019). Today, more than 70% of bacteria have become resistant to one or more antibiotics (Allahverdiyev et al. 2011). That is forcing doctors to increase antibiotic doses, which can cause adverse reactions. And for some severe bacterial infections, there may be no medicine available.

It is urgent to find alternative materials instead of antibiotics to play an antibacterial role. One lead in this direction is that biomolecules immobilized on the surface of nanoscale particles have demonstrated significant antibacterial activity (Brown et al. 2012). The high specific surface area allows nanoscale particles to bind relatively high concentrations of functional ligands or act as carriers for other active substances, enhancing their interaction with target bacteria (Li et al. 2014a).

The nanoscale materials that have demonstrated antibacterial activity include Ag, Cu and Zn ions and zinc and copper oxides (Zhao et al. 2018). Nanoscale gold particles (AuNPs) have shown uniquely advantageous antimicrobial activity. As the least active metal, gold has very stable chemical properties, is non-toxic and has good biocompatibility (Hammer and Norskov 1995). And gold is multivalent; it can bind many types of ligands (Gupta et al. 2016), and AuNPs' very large specific surface area provides abundant sites for binding with target bacteria (Dreaden et al. 2012; Nirmala Grace and Pandian 2007). The antibacterial spectrum is broad. AuNPs have shown antibacterial ability against both Gram-positive and Gram-negative bacteria (Slavin et al.

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2017). Compared with normal antibiotics, AuNPs do not easily produce drug resistance (Zhao et al. 2018) because they target a variety of molecules (DNA and protein) in bacteria, making it difficult for bacteria to establish a system that can defend against all damage.

The preparation and antibacterial properties of AuNPs have been widely studied, but to date no comprehensive summary has been published. This article reviews the progress in recent years in the preparation and antibacterial action of nanoscale gold and its composites, as indicated in Fig. 1. The antibacterial effects of gold nanocomposites are reviewed along with possible mechanisms. Those antibacterial mechanisms mainly involve damaging the cytoderm and biofilms, producing reactive oxygen species and releasing metal ions which induce damage in bacterial cells. The review's aim is to provide a better basis for preparing AuNPs and to disseminate some up-to-date ideas for obtaining more effective antibacterial agents.

Preparation methods

Nanoscale gold particles

Gold has oxidation states between -1 and $+5$, but mainly $+1$ and $+3$. Adding a reducing agent to reduce Au^{3+} or Au^+ to Au^0 is the usual first step in the synthesis of nanoscale gold particles (AuNPs). In addition, the addition of polymers, surfactants or sulfates can enhance the stable dispersion of the particles formed. A large number of incompletely coordinated atoms on the surface of the AuNPs can then bind with numerous ligands to form functionalized gold

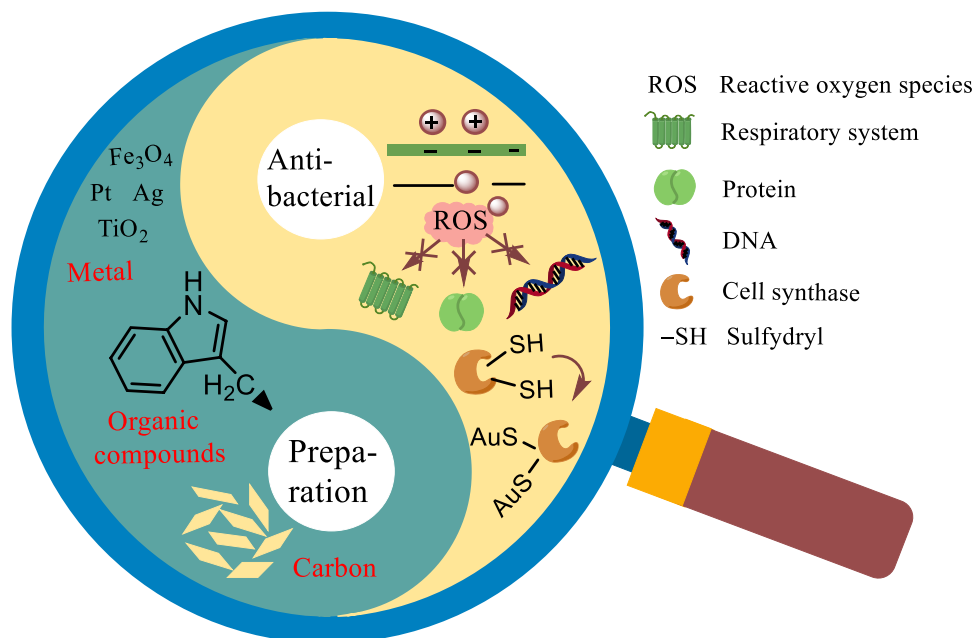
nanoparticles. Increasing the incidence of defects by grinding allows the nanoparticles to absorb and bind more effectively. And today the use of microwaves, electromagnetism or radiation to assist the functionalization of nanoscale gold particles is becoming more widespread. The size, morphology and dispersibility of the gold nanoparticles required vary according to the application. Reaction temperature, reaction time, and the type and amounts of additives all affect the final state of gold nanoparticle synthesis.

An efficient preparation method is the key to obtaining high-quality AuNPs. Chloroauric acid is the raw material most commonly used, but it is very corrosive, requiring the use of plastic or glass equipment. Glassware should be soaked in aqua regia and washed with ultrapure water because foreign impurities may replace the stabilizer and cause aggregation of the nanoparticles. In addition, AuNPs should be stored in a brown bottle protected from light.

The seed growth method

In the seed growth method, chloroauric acid is reduced using sodium borohydride with a protective agent. AuNPs about 1–2 nm in diameter are used as seeds. Growth liquid is added to allow the seed crystals to continue to grow, and AuNPs 10–20 nm in diameter are obtained. The other components of the growth solution are silver nitrate, ascorbic acid and cetyltrimethylammonium bromide. The detailed steps are shown in Fig. 2a. The cetyltrimethylammonium bromide is a stabilizer and a regulator which adjusts the growth rate of the gold crystals along different crystal planes. $HAuCl_4$ solution and sodium borohydride are successively added to the brown-yellow seed solution stabilized

Fig. 1 A brief diagram of the preparation of functionalized gold nanoparticles along with their antibacterial properties



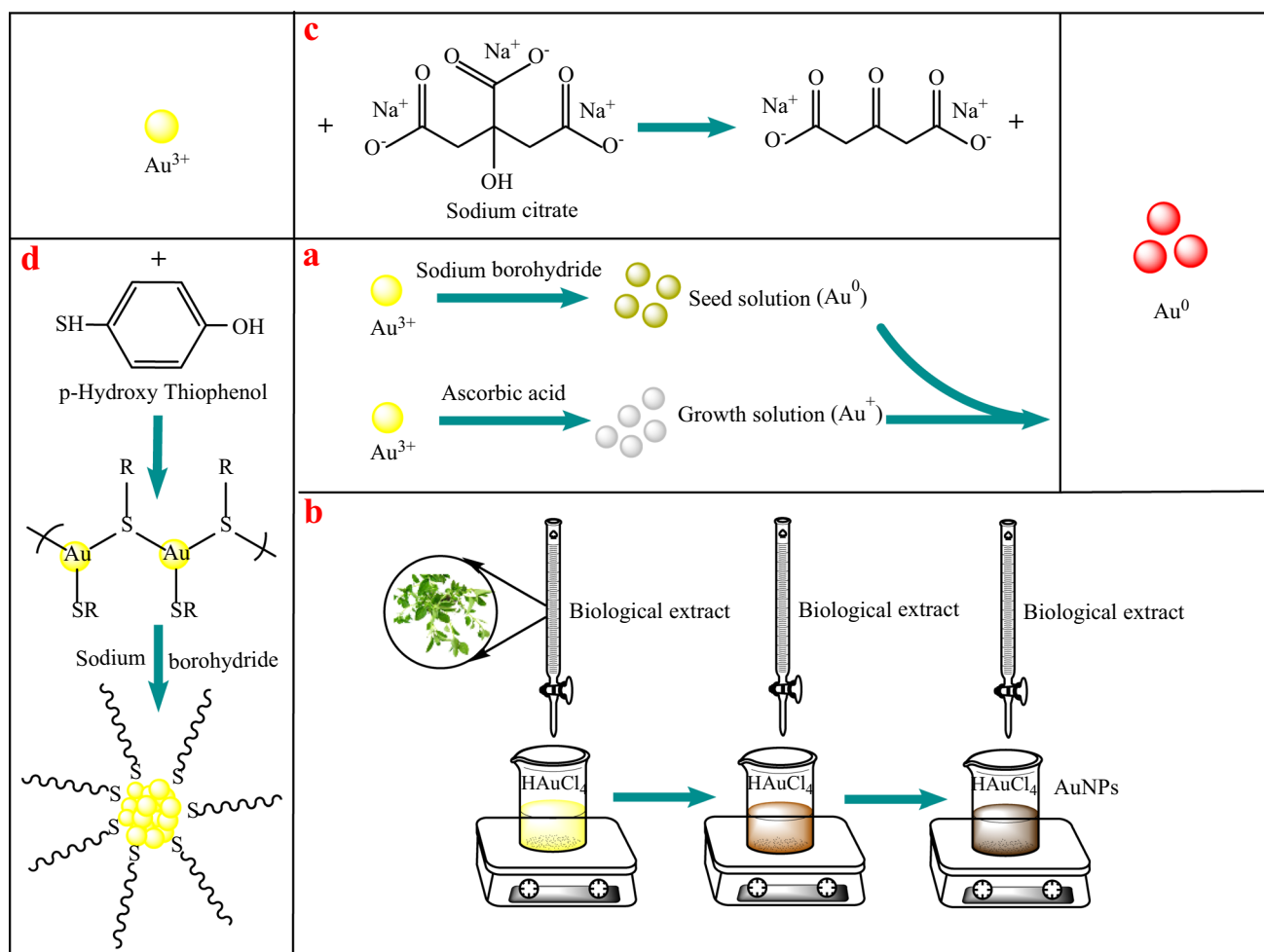


Fig. 2 Preparation of gold nanoparticles (AuNPs). **a** The seed growth method; **b** biological extract synthesis; **c** the sodium citrate reduction method; **d** the Brust–Schiffrin method

by cetyltrimethylammonium bromide with vigorous stirring over about 2 h. Sodium borohydride is a strong reducing agent which reduces Au^{3+} directly to Au^0 to obtain the seed solution. The cetyltrimethylammonium bromide is stirred into a certain volume of AgNO_3 solution at room temperature, and then, HAuCl_4 solution is added. At this time, the solution appears bright yellow. Finally, a certain volume of ascorbic acid solution, a weak reducing agent, is added to prepare a colorless growth solution. Au^{3+} is reduced to Au^+ . Finally, the seed solution is poured into the growth solution and mixed well and left to grow steadily for about 16 h, during which time the solution turns soil red. At this point, Au^0 acts as a catalyst to reduce Au^+ to Au^0 in the presence of ascorbic acid, so that the auric nuclei continue to grow slowly (Li et al. 2017).

Li and his colleagues describe preparing gold nanorods using the seed growth method (Li et al. 2017). Studies have shown that when the concentration of ascorbic acid is 0.60 mM, the concentration of silver nitrate is 0.08 mM, a

16 h reaction time generates the best gold nanorods with a large aspect ratio. A group led by Gonzalez-Rubio controlled the size and morphology of gold nanorods by optimizing the seed growth stage and improved the reproducibility of the preparation (Gonzalez-Rubio et al. 2019). One advantage of the seed growth method is that AuNPs of various sizes and morphologies can be obtained through appropriate regulation of the proportions of seed crystals and silver nitrate, the ascorbic acid concentration, the reaction time and temperature. The seed growth method is particularly suitable for systems that have strict particle size and morphology requirements.

Biological extract synthesis

Biological extract synthesis is a relatively green methodology which has emerged in response to the toxicity of some of the compounds added in other syntheses. It uses biological extracts as stabilizers, reducing agents and capping agents

to synthesize highly dispersible and stable bioactive AuNPs. It has the advantages of safety, mild reaction conditions, simple operation and low cost and can be operated on a large scale without additional reducing agents and stabilizers. The detailed preparation steps of a biological extract synthesis are shown in Fig. 2b.

The biological extract is obtained through a series of treatments such as washing, water bath heating and paper filtration. Reducing substances such as vitamins, sugars and hydroxyl groups are extracted in this way from grapefruit skins and used as reducing agents and stabilizers (Yuan et al. 2017). The biological extract is added dropwise to a solution of HAuCl_4 and mixed well. A change in color from light brown to dark brown indicates the formation of AuNPs. Yuan's group successfully synthesized gold with particle size of 10 nm in this way. Their AuNPs showed bacteriostatic effectiveness with both *E. coli* and *S. aureus*, and the bacteriostatic effect increased with the AuNP concentration. AuNPs have also been prepared using extracts of *Sueda frutescens* (Khan et al. 2017), *longan* juice (Khan et al. 2016) and *mushroom* (Lee et al. 2015).

Chemical reduction

The principle of the chemical reduction method is that a reducing agent gives electrons to Au^{3+} so that it is reduced to Au^0 . Common reducing agents are sodium borohydride, ascorbic acid, sodium citrate, H_2O_2 and others. Some reducing agents can also act as stabilizers. Stabilizers and surfactants such as sulfates, phosphorus ligands and cetyltrimethylammonium bromide can effectively forestall agglomeration of the nanoparticles. Surfactants can also control their growth.

The most typical chemical reduction methods are sodium citrate reduction and the Brust–Schiffrin method. Sodium citrate reduction is the most convenient and the most commonly used. It can generate spherical gold particles between 10 and 50 nm in diameter. However, it is difficult to prepare smaller particles. As shown in Fig. 2c, sodium citrate is added dropwise to a boiling aqueous solution of chloroauric acid. After about 25 s, the solution turns pale blue, indicating that it has been nucleated. It becomes bright red after 70 s, and monodisperse spherical particles are formed. Frens' experiments showing that the reduction of chloroauric acid is basically complete after boiling for 5 min. Longer heating or additional citrate produces no substantial change to the suspension (Frens 1973).

The advantage of the sodium citrate reduction method is that highly dispersed AuNPs of different particle sizes can be obtained simply by changing the amount of sodium citrate added. The disadvantage is that the nanogold interface obtained by this method is not clean due to the

decomposition of sodium citrate during the synthesis (Panahi et al. 2017).

The Brust–Schiffrin method (Brust et al. 1955) is also known as the two-phase method. Chloroauric acid solution and p-mercaptophenol are dissolved in methanol. The addition of acetic acid prevents protonation of the p-mercaptophenol. Tetraoctylammonium bromide is used as a phase transfer agent to transfer HAuCl_4 from the aqueous to the organic phase. Sodium borohydride, a strong reducing agent, is added in the presence of dodecyl mercaptan, and rapid browning of the solution marks the formation of gold clusters. The particle size varies with the ratio of gold to dodecyl mercaptan. Dodecyl mercaptan is a surfactant. It is amphiphilic and so can be adsorbed on the particles' surface. Nanoparticles coated with surfactant can remain stable in a solid or liquid state for a long time. This method is diagrammed in Fig. 2d.

AuNPs obtained by the Brust–Schiffrin method are small and very stable. The isolated gold nanoparticles can be re-dispersed in organic solvents. The disadvantage is that the preparation method is complicated.

Metal-modified gold nanoparticles

In recent years, nanoscale particles of metals such as gold, silver, copper, palladium and platinum have been widely used in medical treatment (Annamalai et al. 2013; Ayaz Ahmed et al. 2016; Boomi et al. 2013; Li et al. 2014b; Valodkar et al. 2011; Wang et al. 2016a). However, along with their advantages, metal nanoparticles have shortcomings which limit their practical application. For example, silver nanoparticles have diverse antibacterial mechanisms, but their cytotoxicity limits their application (Wang et al. 2016b). Both platinum and gold nanoparticles are bacteriostatic (Ayaz Ahmed et al. 2016; Li et al. 2014b), but they are costly and material scarcity is a major problem. Combinations of metal nanoparticles can sometimes alleviate these shortcomings. For example, due to the action of strong electron ligands, combining silver and gold can increase the effective concentration range of silver ions (Wang et al. 2016b), enhancing their antibacterial activity. Adding a third metal can sometimes offer further improvement.

The seed growth method

Nanoparticles grown from seed crystals tend to be small and controllable with good dispersibility. The particle size and its dispersion can be controlled by controlling reaction conditions such as the concentration, pH and the temperature of the solution. Emam used Arabic gum as a biosynthetic agent to produce Ag–Au bimetallic nanoscale composite particles using seed-mediated growth techniques, as Fig. 3a shows (Emam 2019). Acacia gum can be used as both a reducing

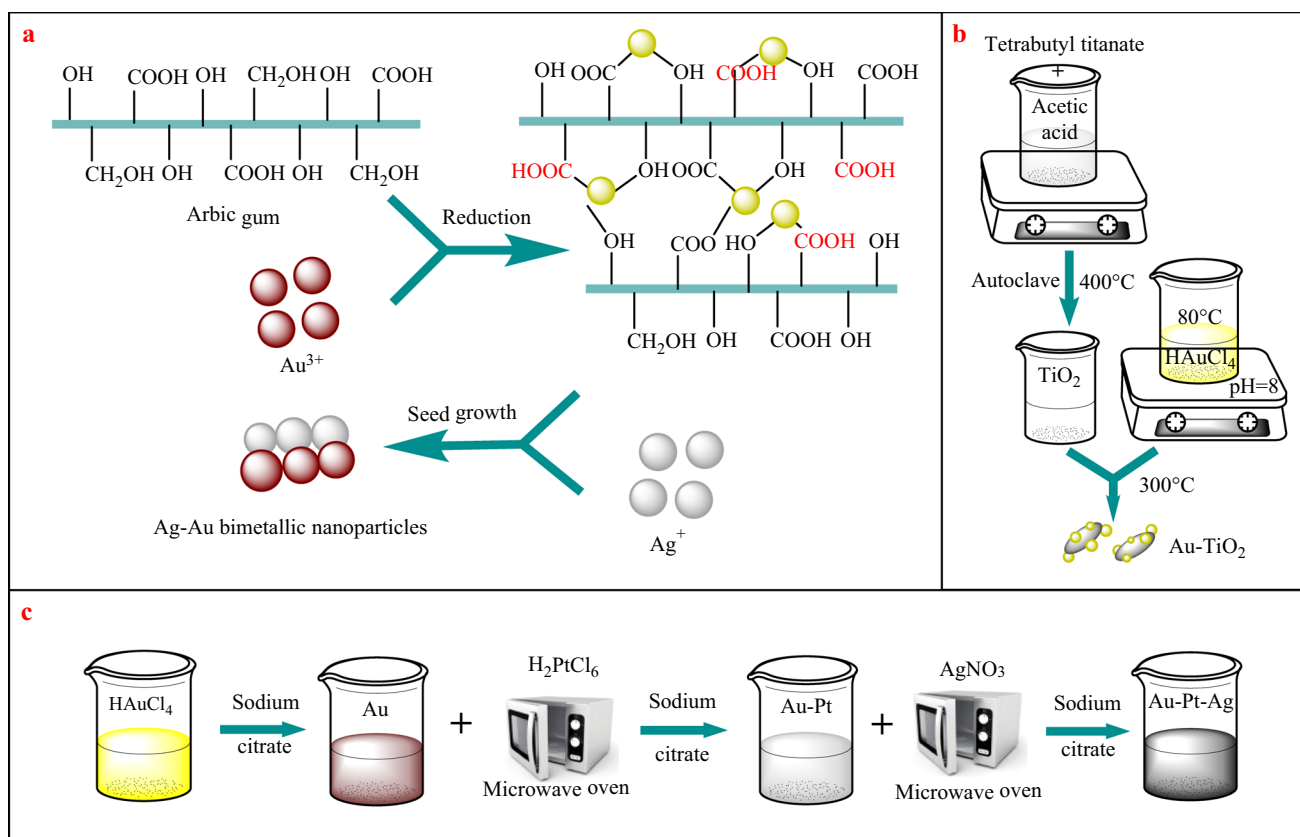


Fig. 3 Typical methods for synthesizing metal-modified nanoscale gold particles. **a** The seed growth method (reprinted with permission from (Emam 2019), Copyright (2019) Springer); **b** the precipitation–deposition method; **c** microwave-assisted continuous chemical reduction

agent for metal ions in producing nanoscale structures and as a crystal growth modifier for nanocomposites. Silver nitrate, gold chloride and sodium hydroxide are added to the prepared Arabic gum with stirring at room temperature or 70 °C. The order of addition of the alkali and metal salts, the concentration of the glue and the reaction temperature all affect the particle size generated. Increasing the reaction temperature reduces the average size of the bimetallic particles from 6.5 to 3.1 nm. Adding alkali after the metal salt increases the size of Ag–Au composite particles from 3.1 to 12.7 nm.

The precipitation–deposition method

A group led by Mishra reports (Mishra et al. 2016) synthesizing Au/Fe₂O₃ composite particles 19–24 nm in diameter by co-precipitation using Fe(NO₃)₃·9H₂O, Na₂CO₃ and HAuCl₄ as raw materials. They mixed aqueous solutions of Fe(NO₃)₃·9H₂O and HAuCl₄ with stirring at 80 °C. An aqueous Na₂CO₃ solution was added dropwise until the precipitation was complete. After the formation of the precipitate, the solution was cooled to room temperature and

aged overnight. After washing, drying and calcining the precipitate at 400 °C for 4 h, the preparation was complete.

Han's laboratory synthesized mesoporous porous TiO₂ by a solvothermal method (Ye et al. 2011), and then deposited Au on the TiO₂ by the precipitation–deposition method (Elmoula et al. 2009; Zanella et al. 2002). The mesogenic porous TiO₂ anatase was prepared from tetrabutyl titanate. 0.2 mL of tetrabutyl titanate was added dropwise to 10 mL of acetic acid under continuous stirring, which was placed in an autoclave and heated at 200 °C for 24 h. Chloroauric acid was heated in an oil bath to 80 °C and 1 g of the mesoporous TiO₂ was added with continuous stirring. After stirring for 5 min, the pH of the suspension was adjusted to 8 with 1 M NaOH solution. After 4 h of vigorous stirring, the suspension was centrifuged, and the precipitate was washed with water and dried. It was then calcined at 300 °C for 4 h and ground for later use. That synthesis is diagrammed in Fig. 3b. Precipitation–deposition is the ideal method for loading gold. The target product can be adjusted by adjusting the concentration of chloroauric acid, the pH and the ratio of gold to the substrate (Moreau et al. 2005).

Microwave-assisted continuous chemical reduction

Adding a third metal can add new dimensions to the properties of bimetallic materials and offer additional scope for their optimization. Yadav and his colleagues successfully synthesized Au/Pt/Ag trimetallic nanoparticles by the microwave-assisted continuous chemical reduction shown in Fig. 3c (Yadav et al. 2018). The gold solution was prepared by sodium citrate reduction. $\text{H}_2\text{PtCl}_6 \cdot x\text{H}_2\text{O}$ solution and sodium citrate solution were added at room temperature; then, the mixture was heated in a microwave oven to yield a Au/Pt bimetallic nanocomposite. An aqueous solution of AgNO_3 was then added and the mixture was microwaved in a loop mode, yielding a black Au/Pt/Ag tri-metal nanocomposite.

Gold nanoparticles modified with organic compounds

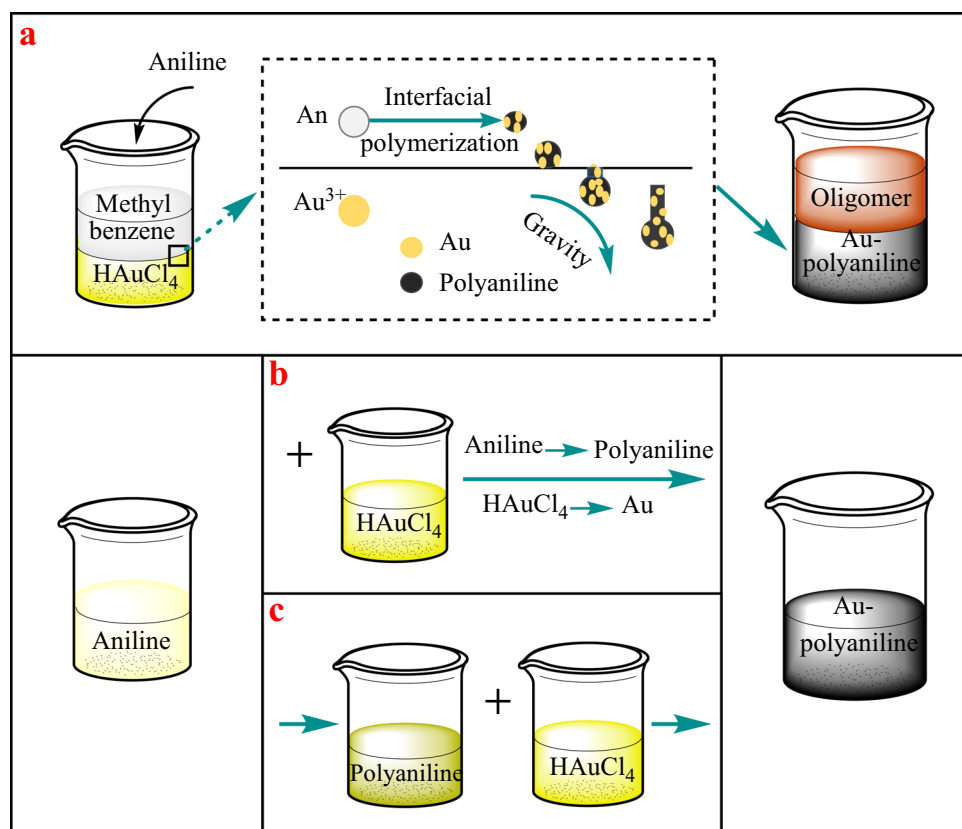
Macromolecules can stabilize nanoscale gold particles (AuNPs) and also give them additional functionality. The physicochemical method for obtaining polymer-modified gold nanoparticles has been extensively studied (Dzhardimalieva et al. 2011; Feuz et al. 2012; Raula et al. 2003). There are three generic methods for preparing organic-coated gold nanoparticles.

The interface polymerization method

The interfacial polymerization method is a two-phase system in which an aqueous solution of toluene and chloroauric acid is the oil phase and there is an aqueous phase. The size and morphology of the composite material can be adjusted by controlling the amount of the reactants and the reaction time. The specific preparation process is shown in Fig. 4a. The toluene organic phase is added to the aqueous chloroauric acid solution to form a two-phase interface. Aniline solution is added, and the reaction immediately occurs at the interface, producing a purple-red color which darkens subsequently. Eventually, a black substance appears at the bottom, an Au–polyaniline nanocomposite.

Experiments conducted by Jin's group (Jin et al. 2016) show that when using interfacial polymerization to synthesize such materials, controlling the amount of chloroauric acid can change the morphology of the Au–polyaniline composite. With 5 mL of 10 mM chloroauric acid nanospheres formed. With 1 mL of 10 mM chloroauric acid lollipop-shaped particles formed. AuNPs modified with organic monomers can be used for monitoring plasma-driven reactions using surface-enhanced Raman imaging. The interface polymerization method does not require adding any reducing agent. Organic monomers acting as ligands can also serve as reducing agents to directly reduce

Fig. 4 Typical synthesis for gold nanoparticles (AuNPs) modified with an organic compound. **a** Interface polymerization; **b** one-step polymerization; **c** two-step polymerization



metal ions to metal nanoparticles because the reduction potential of gold-containing compounds is higher than that of organic monomers.

One-step polymerization

The one-step method is another common method for preparing AuNPs modified with organics. Unlike the interfacial polymerization method, in the one-step method the organic compound and the chloroauric acid solution are mixed directly, and the reaction conditions are adjusted to obtain the target product. Li's group ultrasonically mixed an ethanol solution of aniline with HAuCl_4 solution to obtain a wine-red suspension (Li et al. 2016a). Oxidative polymerization of the aniline formed polyaniline, while the chloroauric acid was reduced to metallic gold, as indicated in Fig. 4b. After centrifugation and purification, an Au–polyaniline composite was obtained.

Zhao's group used indole derivatives as reducing agents and ligands to synthesize indole derivative-modified gold nanoparticles in one step (Zhao et al. 2018). Tween was added to the chloroauric acid solution, stirred to uniformity, and the reaction was continued by adding an indole solution to obtain indole derivative-modified gold nanoparticles. The synthesis of AuNPs modified with other indole derivatives such as tryptophan, 5-aminoindole was consistent with the basic indole derivative-modified gold nanoparticles method. The one-step method involves no complicated preparation steps, avoids material loss and damage and maximizes the original properties of the material. However, the Au–polyaniline composite prepared by this method has a low molecular weight insufficient for some purposes and low conductivity.

Two-step polymerization

There is also a two-step process. The first step is to prepare a polyaniline solution with reducing properties. The second is to reduce the chloroauric acid to obtain Au–polyaniline nanocomposite. A group led by Ma first polymerized aniline; then, HAuCl_4 was reduced on polyaniline nanotubes to generate modified AuNPs on the nanotubes (Ma et al. 2016). This is sketched in Fig. 4c. The two-step method can also be used to prepare AuNPs in the first step. The second step is then to mix AuNPs and aniline to obtain Au–polyaniline nanocomposites by in situ polymerization. Compared with the one-step method, the two-step method can better regulate the product's morphology and particle size. However, the force binding the gold nanoparticles and the polyaniline is weak, and the gold nanoparticles easily fall off.

Carbon-modified gold nanoparticles

Little has been published about the idea of modifying gold nanoscale particles with inorganic carbon. There is, however, a sol–gel method and a one-step in situ growth method. Combining inorganic carbon with nanoscale gold particles gives it more applications by improving the dispersibility, fluorescence and biocompatibility of gold nanoparticles.

The sol–gel method

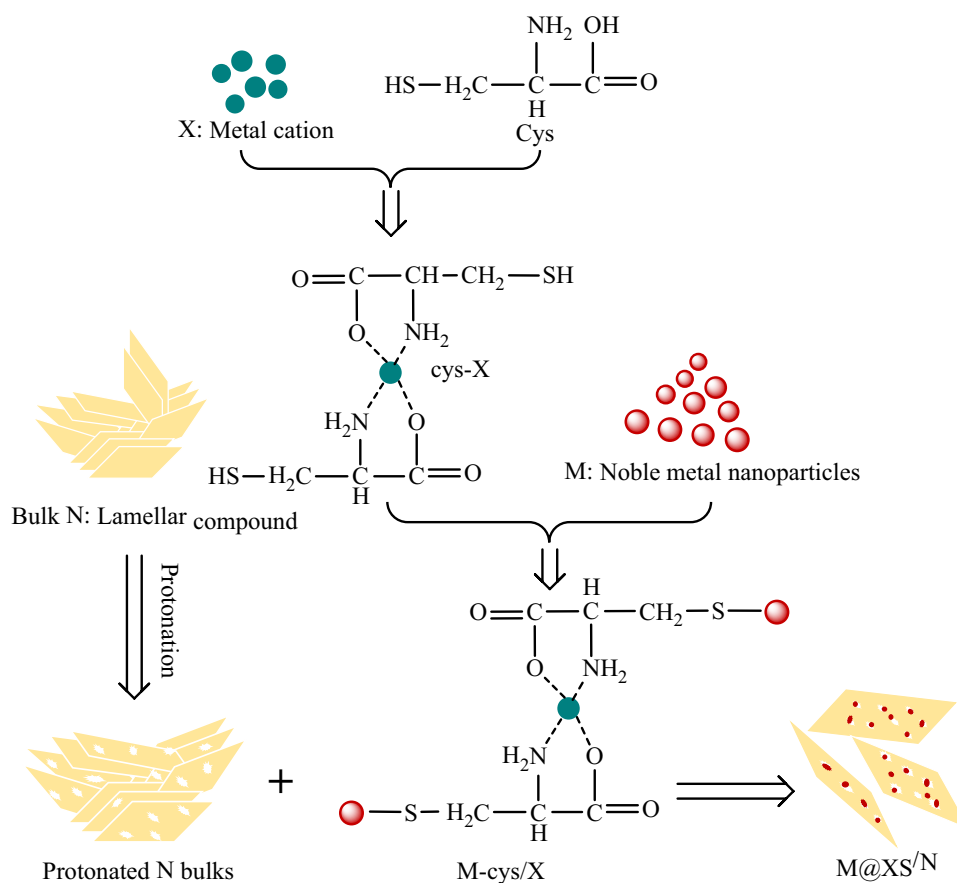
A group led by Wang has successfully synthesized the composite Au@CdS/g- C_3N_4 (Wang et al. 2018). Au colloid was first prepared by the citrate reduction method. A suspension of cysteine-capped Au nanoparticles was prepared by mixing cysteine into a suspension of the nanoparticles. Cysteine and $\text{Cd}(\text{NO}_3)_2$ were dissolved in deionized water to obtain a cysteine/ Cd^{2+} solution. A certain amount of Au colloid was then added to the cysteine/ Cd^{2+} solution with vigorous stirring. The protonated graphitic carbon nitride (g- C_3N_4) expanded body was added, stirred, and the mixture was heated to 130 °C for 6 h for hydrothermal reaction. After washing and drying, Au@CdS/g- C_3N_4 composite was obtained.

The structure of the composite is regulated by controlling the mass ratio of the precursors. This method is suitable for the synthesis of various M@XS/N multi-component complexes. The synthesis steps are shown in Fig. 5. In the figure, M stands for any noble metal nanoparticle, XS stands for sulfide, and N can be a compound with a lamellar structure (such as g- C_3N_4 or graphene). Note, however, that the pure M@XS product is obtained in only low yield, so the method may not be suitable for large-scale use.

A one-step in situ growth method

Combination with inorganic carbon affects the catalytic activity of nanoscale gold particles (AuNPs). The g- C_3N_4 is a polymeric semiconductor with good thermal and chemical stability. It has a wide absorption spectrum and can effectively activate oxygen molecules to produce superoxide radicals. Therefore, g- C_3N_4 has been widely used as visible light-activated catalyst. Fu and his colleagues report uniformly loading 2.8 nm AuNPs on the surface of g- C_3N_4 nanosheets using a one-step in situ growth method (Fu et al. 2017). The g- C_3N_4 nanosheet is first prepared using an ultrasonic stripping technique. The chloroauric acid solution is then added to a dispersion of g- C_3N_4 , and sodium borohydride solution is added with stirring to continue the reaction. After centrifugal drying, the Au/g- C_3N_4 product is obtained. The method is simple and can yield small AuNPs. Studies have shown that the photocatalytic activity of Au/g- C_3N_4 driven by

Fig. 5 Preparation of M@XS/N nanocomposite by the sol–gel method (Cys, cysteine)



visible light is significantly improved compared with that of ordinary gold. This may be attributed to the interaction between gold and g-C₃N₄ causing charge transfer.

Green synthesis using biological extracts

Carbon quantum dots are highly dispersed carbon nanoparticles. They have useful optical properties and good biocompatibility. Very small gold clusters (<2 nm) have enhanced fluorescence attributed to the oscillation of free electrons within them. Venkateswarlu's group reports that the synthesis of Au/Carbon quantum dots nanocomposites is promoted by using onion leaf extract as a reducing agent (Venkateswarlu et al. 2019). Onions contain flavonoids and phenolic compounds that act as reducing agents, stabilizers and carbon precursors. The specific preparation steps are as follows. The onion leaves are water-washed and filtered to obtain an extract. The extract is poured into a freshly prepared mixture of chloroauric acid and glutathione and heated in a microwave oven. Freeze-drying then yields the target product. The addition of carbon precursors stabilizes the product for at least 300 days with excellent detection limits for Hg²⁺.

Antibacterial properties of functionalized gold nanoparticles and the mechanisms involved

The different preparation methods lead to different nanoparticle sizes and size distributions. That in turn affects their antibacterial properties. Differences in surface modification can affect the antibacterial properties of nanoparticles in two ways. One is to change the gold nanoparticles' morphology, structure and dispersion. The second is to increase their antibacterial effectiveness. For example, the molecules with special optical, electrochemical or biological activity can be connected to the surface of gold nanoparticles by some synthetic methods (Liu and Lammerhofer 2019).

Size, dispersibility and antibacterial activity

Gold's stability and low toxicity and the high specific surface area and easy functionalization of nanoparticles have meant that nanoscale gold particles (AuNPs) have been widely studied and applied as an effective antibacterial

Table 1 Antibacterial properties of gold nanoparticles

Method	Composition	Size (nm)	Additive concentration	Bacteria types	Assessment methods	Antibacterial effect	References
Green synthesis using plant extracts	AuNPs	16	–	Conventional bacteria	Zone of inhibition	<i>S. epidermidis</i> : 30 mm <i>E. coli</i> : 26 mm	Boomi et al. (2020)
Bioreduction approach	AuNPs	22.8	–	Conventional bacteria	–	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>E. coli</i> , <i>P. aeruginosa</i> : strong inhibitory activity against all bacteria	Vanaraj et al. (2017)
Green synthesis using plant extracts	AuNPs	–	–	Conventional bacteria	Zone of inhibition	<i>E. coli</i> : 14 mm <i>S. aureus</i> : 16 mm <i>B. subtilis</i> : 12 mm	Lee et al. (2015)
Seeded growth method	Au nanorods	10	2×10^{-4} – $50 \mu\text{g mL}^{-1}$	Conventional bacteria	MIC	<i>S. aureus</i> : $0.008 \mu\text{g mL}^{-1}$ <i>L. monocytogenes</i> : $0.0002 \mu\text{g mL}^{-1}$ <i>E. coli</i> : $0.05 \mu\text{g mL}^{-1}$ <i>S. typhimurium</i> : $0.2 \mu\text{g mL}^{-1}$	Lanh et al. (2015)
Green synthesis using plant extracts	AuNPs	3.87–77.13	–	Conventional bacteria	Zone of inhibition	<i>E. coli</i> : 17–16 mm <i>K. pneumoniae</i> : 17–16 mm <i>MRSA</i> : 17–16 mm <i>S. aureus</i> : 13 mm <i>P. aeruginosa</i> : 13 mm Powder AuNPs (G. elongate) <i>E. coli</i> : 13.5 mm <i>K. pneumoniae</i> : 13 mm	Abdel-Raouf et al. (2013)

AuNPs nanoscale gold particles, MIC minimum inhibitory concentration, MRSA methicillin-resistant *S. aureus*

agent (Connor et al. 2005; Dizaj et al. 2014; Gupta et al. 2016). The antibacterial properties of AuNPs are shown in Table 1. The size and dispersibility of nanoparticles are important for their antibacterial effectiveness. Generally speaking, smaller AuNPs 2–15 nm in diameter is more used in tissue immunology, biochemistry and high-powered microscopy. In environmental testing, DNA testing and drug delivery, medium-sized AuNPs with a diameter of 20–60 nm are mostly used. Larger AuNPs with a diameter of 80–250 nm are used in medical, electrical and X-ray optics (Shah et al. 2015). With the morphology of gold nanoparticles changes from dispersed small particles to large aggregates, the color of a suspension of them changes from red to blue.

Silver nanoparticles follow the rule that the smaller the size, the better the antibacterial effect, and gold nanoparticles also follow this pattern. Vanaraj's group used a methanol extract of *C. ternatea* leaves to prepare 100 nm AuNPs (Vanaraj et al. 2017). In an anti-biofilm activity experiment

against *Pseudomonas aeruginosa*, the rate of biofilm formation was inhibited 94.4%, but only after the concentration of AuNPs reached $100 \mu\text{g/mL}$. Lanh and his colleagues used a seeding method to produce gold nanorods 10 nm in diameter (Lanh et al. 2015), and studies have shown that the minimum inhibitory concentrations of gold nanorods against *E. coli*, *S. Typhimurium*, *S. aureus* and *L. monocytogenes* are $0.05 \mu\text{g/mL}$, $0.2 \mu\text{g/mL}$, $0.008 \mu\text{g/mL}$ and $0.0002 \mu\text{g/mL}$, respectively.

Emam prepared Au–Ag bimetallic nanocomposites with different particle sizes. Studies have shown that smaller bimetallic nanocomposites exhibit better antibacterial activity. Bimetallic particles 3.1 nm in diameter were observed to eliminate 83.2–87% of bacteria after 6 h. Under the same conditions, however, the bacteriostatic rate of bimetallic nanocomposites with an average particle size of 22.1 nm was only 60.9% (Emam 2019). In addition, small gold nanoclusters 1–2 nm in equivalent diameter can be formed by controlling the reaction

conditions. Bacteria can take in such small clusters with nutrients and they then interfere with the bacteria's normal metabolism. Active oxygen species accumulate in the bacteria and the stability of their cytomembranes is reduced. Cell death is the likely result.

The effect of dispersibility on the antibacterial properties of AuNPs cannot be ignored. The antibacterial advantages of small nanoparticles are limited by their dispersibility. Generally, the proportion of surface atoms increases rapidly when the size of nanoparticles is below 10 nm. The atoms concentrated on the particle's surface are highly active and tend to stabilize by binding with other atoms. Any aggregation of nanoparticles reduces their contact area with bacteria, which weakens their antibacterial properties. Other studies have shown that small gold nanoparticles can enter cells by binding to the pore proteins and changing the pathway of porin (Wigginton et al. 2010). Reducing the particle size and increasing the dispersibility therefore help to improve nanoparticles' antibacterial properties.

Various surfactants, stabilizers and reducing agents are usually used in the preparation of AuNPs. The resulting particle size is related to the type and amount of reducing agent. Common reducing agents include sodium citrate, sodium borohydride, ascorbic acid, hydroxylamine hydrochloride, amino acids, H_2O_2 and others (Liu and Lammerhofer 2019). White phosphorus or ascorbic acid is usually used to prepare AuNPs 5–12 nm in diameter. It is difficult for ascorbic acid to reduce trivalent gold particles to zero, but it can reduce the valence to one. Therefore, ascorbic acid is mainly used in the growth solutions of the seeded growth method. For the preparation of AuNPs with particle size larger than 12 nm, sodium citrate is used. Sodium citrate has weak reducing properties, so larger AuNPs can be prepared, and it acts as a stabilizer at the same time. Sodium borohydride is a strong reducing agent, which dissociates hydrogen ion during the reaction process. Sodium borohydride will show obvious nucleation during the reduction process. It cannot be used together with a strong stabilizer, or no large nanoparticles will be obtained. The size of AuNPs is inversely proportional to the amount of reductant used (Panahi et al. 2017).

In order to maintain stable nanoparticle dispersion, physical and chemical dispersion methods are employed. Chemical dispersion requires selection of an appropriate dispersant, normally a surfactants or polymer, to control particle interactions. Surfactants are mainly used as stabilizers, but they can also control the size and morphology of nanoparticles. Physical dispersion mainly depends on mechanical and ultrasonic dispersion. In addition, the electrostatic repulsion effect of the charged ligand can also achieve the purpose of dispersion (Shah et al. 2015).

Surface functionalization and antibacterial activity

Single nanomaterials cannot meet the growing functional needs of practical applications. Compounding multiple materials can realize better regulation of the material's structure and function. Nanoscale gold itself is expensive and relatively scarce. Combining it with metals, organic compounds or inorganic carbon can both reduce the cost and increase its functionality. In recent years, bimetallic and trimetallic nanoparticles have been widely used for their unique properties (Karthikeyan and Loganathan 2012; Li et al. 2016b; Luo et al. 2017; Pandey and Pandey 2016; Rao and Paria 2015; Venkatesan and Santhanalakshmi 2010; Wang and Yamauchi 2011; Wang et al. 2016b; Yang et al. 2017). The antibacterial properties of metal-modified nanoscale gold particles (AuNPs) are shown in Table 2. Some organic compounds also exhibit good antibacterial activity. And using inorganic carbon as a supporting material in synthesizing AuNPs can effectively prevent the particles' agglomeration. The antibacterial properties of AuNPs modified with organic compounds and inorganic carbon are shown in Table 3.

Metal-modified gold nanoparticles

The antibacterial properties of AuNPs can be improved by combining them with other metals, metal oxides or metal hydroxides. Au and Ag at low concentrations are less toxic to normal cells, but more lethal to bacteria. Therefore, silver and gold composites have been widely studied as antimicrobial agents. The diameter of the inhibition zone of the 10 nm Au–Ag nanocomposite prepared by Bankura was 24 nm against *B. subtilis*, 21 nm against *B. cereus*, 17 nm against *E. coli* and 20 nm against *P. aeruginosa*. And the antibacterial action was superior to that of gold nanoparticles alone (Bankura et al. 2014). Another study showed that Au–Pt nanoaggregates have enhanced antibacterial potential compared to Au and Pt single metal nanoparticles (Britto Hurtado et al. 2020).

Ding's experiments showed that Au@AgNPs had strong antibacterial activity against *S. aureus*, with a minimum inhibitory concentration (MIC) of 7.5 pM (Ding et al. 2017). This is because positively charged Au@Ag NPs can aggregate with the surface of negatively charged bacteria, producing strong two-photon photoluminescence. That has a strong photothermal effect, so Au@AgNPs can effectively remove 85% of a bacterial biofilm in 4 min under near-infrared radiation (Ding et al. 2017). Nanostructures with a photothermal effect convert light energy into heat and kill bacteria by local heating. Common photocatalytic nanomaterials include ZnO, TiO_2 , Fe_2O_3 and others.

Gholap's group used a hydrothermal method to prepare Au@ZnO composite at a concentration of 20 $\mu\text{g}/\text{mL}$ which reduced the growth of *Bacillus subtilis* by 99.9% (Gholap

Table 2 Antibacterial properties of metal-modified gold nanoparticles

Method	Composition	Size (nm)	Additive concentration	Bacteria types	Assessment methods	Antibacterial effect	References
One-pot method	Au/Ag clusters	Au: 1.5–3.5 Au/Ag: 102 ± 13	–	Conventional bacteria	Zone of inhibition	<i>P. aeruginosa</i> : 31.9 mm	Wang et al. (2020)
Ionic liquid-supported hydrothermal process	Ag–Au/CeO ₂	5–15	25, 50, 100 µg mL ⁻¹	Conventional bacteria	Zone of inhibition	<i>E. coli</i> 25 µg mL ⁻¹ ; 20 mm 50 µg mL ⁻¹ ; 25 mm 100 µg mL ⁻¹ ; 29 mm <i>S. aureus</i> 25 µg mL ⁻¹ ; 23 mm 50 µg mL ⁻¹ ; 26 mm 100 µg mL ⁻¹ ; 32 mm	Nithya and Sundrarajan. (2020)
Chemical reduction	Fe ₃ O ₄ –Au	18	–	Conventional bacteria	Zone of inhibition	<i>E. coli</i> : 12 mm <i>P. aeruginosa</i> : 12 mm	Arockia Jency et al. (2020)
Green synthesis using biological extracts	Ag–Au	–	–	Conventional bacteria	Zone of inhibition	<i>K. Planticola</i> : 13 mm <i>B. subtilis</i> : 14 mm	Lagashetty et al. (2019)
Light reduction	Au/ZnO	30–33	50 µg mL ⁻¹ 100 µg mL ⁻¹	Conventional bacteria	Survival percentage (%)	<i>S. aureus</i> 50 µg mL ⁻¹ ; 20% 100 µg mL ⁻¹ ; 10% <i>E. coli</i> 50 µg mL ⁻¹ ; 13% 100 µg mL ⁻¹ ; 3%	He et al. (2014)
Chemical reduction	AuRh AuIr AuRu AuOs AuRh	10–20	8 µg mL ⁻¹	Conventional bacteria, drug-resistant bacteria	MIC	<i>E. coli</i> AuRh, AuIr, AuRu, AuOs: 7, 12, 28, 55 µg mL ⁻¹ 1:1 AuRh <i>E. coli</i> , polymyxin-resistant <i>E. coli</i> , <i>K. pneumoniae</i> , <i>pneumoniae</i> , <i>polymyxin-resistant K. pneumoniae</i> : 7 µg mL ⁻¹ <i>MDR E. coli</i> , <i>MDR K. pneumoniae</i> , <i>P. aeruginosa</i> : 14 µg mL ⁻¹ <i>MDR A. baumannii</i> : 8 µg mL ⁻¹	Zhao et al. (2018)

Table 2 (continued)

Method	Composition	Size (nm)	Additive concentration	Bacteria types	Assessment methods	Antibacterial effect	References
Green, microwave-assisted continuous chemical reduction	Au–Pt–Ag	20–40	–	Conventional bacteria	MIC	<i>S. aureus</i> : 31.25 µg mL ⁻¹ <i>E. faecalis</i> (clinical isolate): 15.625 µg mL ⁻¹ <i>E. coli</i> : 15.625 µg mL ⁻¹ <i>S. typhi</i> : 15.625 µg mL ⁻¹ <i>Klebsiella</i> : 15.625 µg mL ⁻¹	Yadav et al. (2018)
Seeded growth	Au–Ag	3.1	–	Conventional bacteria	Bacterial reduction (%)	<i>E. coli</i> : 83.2% <i>S. aureus</i> : 87%	Emam. (2019)
Magnetron sputtering	Au–TiO ₂ -nanotubes	10–20	–	Conventional bacteria	Bacteria inactivation rate (%)	<i>S. aureus</i> : 99% in 1 day 74% in 21 days	Wang et al. (2017a)
Polyethyleneimine auxiliary connection method	Fe ₃ O ₄ /Au–Ag	155	10, 20, 30, 40, 50 µg mL ⁻¹	Conventional bacteria	MIC	<i>E. coli</i> : 20 µg mL ⁻¹ <i>S. aureus</i> : 50 µg mL ⁻¹	Wang et al. (2016c)
Sodium citrate reduction process	Au–Ag	23	9 × 10 ⁻¹³ – 3 × 10 ⁻¹¹ mol L ⁻¹	Conventional bacteria	MIC	<i>S. aureus</i> : 7.5 × 10 ⁻¹² mol L ⁻¹	Ding et al. (2017)
Phytosynthesis	Au–Ag	Au:Ag molar ratio 1:1 17 1:3 14 5:1 20	–	Conventional bacteria	Zone of inhibition	<i>E. coli</i> : 28 mm <i>S. aureus</i> : 18 mm	Vilas et al. (2016)
Hydrothermal method	Au–ZnO	1000–2000	20 µg mL ⁻¹	Conventional bacteria	Bacterial reduction (%)	<i>B. subtilis</i> : 99.9% <i>E. coli</i> : 0	Gholap et al. (2016)
Hot sol method	Au–TiO ₂	10–30	–	Conventional bacteria	Survival percentage (%)	<i>E. coli</i> 0.5%, 1%, 3%, 5% Au/TiO ₂ : 44.2%, 32.4%, 52.7%, 4.8%	Zhang et al. (2016)
Chemical reduction method	Au–Ag	10	100 µg mL ⁻¹	Conventional bacteria	Zone of inhibition	<i>B. subtilis</i> : 24 mm <i>B. cereus</i> : 21 mm <i>E. coli</i> : 17 mm <i>P. aeruginosa</i> : 20 mm	Bankura et al. (2014)
One-step method	m-PEG–Au–Ag	18 ± 2.3	>2.5 µg mL ⁻¹ 1.25 µg mL ⁻¹	Conventional bacteria	Inhibition ratio(%) MIC	<i>S. aureus</i> IR > 50% <i>E. coli</i> : 1.25 µg mL ⁻¹	Huo et al. (2014)

MIC minimum inhibitory concentration, MDR multi-drug resistant, m-PEG Methoxy polyethylene glycol

Table 3 Antibacterial properties of gold nanoparticles modified with organic compounds and carbon

Method	Composition	Size (nm)	Additive concentration	Bacteria types	Assessment methods	Antibacterial effect	References
Chemical reduction	AuNPs/Gentamycin sulfate	2.86	–	Conventional bacteria; drug-resistant bacteria	MIC	<i>E. coli</i> : 1 $\mu\text{g mL}^{-1}$ <i>S. aureus</i> : 4 $\mu\text{g mL}^{-1}$ <i>S. aureus</i> : methicillin-resistant 128 $\mu\text{g mL}^{-1}$	Zou et al. (2020)
Green synthesis using biological extracts	Clerodendrum-Au	5.82	250 $\mu\text{g mL}^{-1}$	Conventional bacteria	Zone of inhibition	<i>E. coli</i> : 16 mm <i>S. aureus</i> : 13 mm <i>B. subtilis</i> : 14 mm <i>A. niger</i> : 15 mm <i>A. flavus</i> : 20 mm	Khan et al. (2020)
Chemical reduction	Au-DAPT-BSA	4.11	–	Conventional bacteria; drug-resistant bacteria	MIC	<i>E. coli</i> : 1 $\mu\text{g mL}^{-1}$ <i>S. aureus</i> : 16 $\mu\text{g mL}^{-1}$ MDR <i>E. coli</i> : 1 $\mu\text{g mL}^{-1}$ MRSA: 16 $\mu\text{g mL}^{-1}$	Sun et al. (2019)
One-step method	Au-5-aminopurine Au-tryptophan	5–10	8 $\mu\text{g mL}^{-1}$	Conventional bacteria; drug-resistant bacteria	MIC	MDR <i>E. coli</i> : 2 $\mu\text{g mL}^{-1}$ <i>polymyxin-resistant E. coli</i> : 2 $\mu\text{g mL}^{-1}$ <i>K. pneumoniae</i> : 2 $\mu\text{g mL}^{-1}$ <i>E. coli</i> : 4 $\mu\text{g mL}^{-1}$ <i>P. aeruginosa</i> : 4 $\mu\text{g mL}^{-1}$ MDR <i>K. pneumoniae</i> : 4 $\mu\text{g mL}^{-1}$ <i>polymyxin-resistant K. pneumoniae</i> : 4 $\mu\text{g mL}^{-1}$ MDR <i>A. baumannii</i> : 4 $\mu\text{g mL}^{-1}$	Zhao et al. (2018)
One-step method	Au/AgNPs@Van	5–9	30, 60, 120, 240 nmol mL ⁻¹	Conventional bacteria	MIC	Au/AgNPs@Van-1 (Au content 25%): 60 nmol mL ⁻¹ Au/AgNPs@Van-2 (Au content 33%): 30 nmol mL ⁻¹ Au/AgNPs@Van-3 (Au content 50%): 30 nmol mL ⁻¹	Lu et al. (2017)

Table 3 (continued)

Method	Composition	Size (nm)	Additive concentration	Bacteria types	Assessment methods	Antibacterial effect	References
Radiation-assisted diffusion	Au-Polycarbonate	110	–	Conventional bacteria	Zone of inhibition	<i>S. aureus</i> : 1.5 ± 0.12 mm <i>E. coli</i> : 1.2 ± 0.11 mm Control (Tetracycline) <i>S. aureus</i> : 12 ± 1.06 mm <i>E. coli</i> : 11 ± 0.35 mm	Hareesh et al. (2015)
Chemical reduction	Au-Cefradine	13, 40, 150 HAuCl ₄ (10 ⁻⁴ M, 5 × 10 ⁻⁴ M, 10 ⁻³ M)	64, 32, 16, 8, 4, 2, 1, 0.5 µg mL ⁻¹	Conventional bacteria	MIC	Cefradine: 8 µg mL ⁻¹ Au-Cefradine > 64 µg mL ⁻¹	Khandelwal et al. (2015)
Chemical oxidation polymerization	Polyaniline-Ag-Au	10	100 µg mL ⁻¹	Conventional bacteria	Zone of inhibition	<i>Streptococcus sp.</i> : 28 mm <i>Staphylococcus sp.</i> : 29 mm <i>E. coli</i> : 31 mm <i>Klebsiella sp.</i> : 28 mm	Boomi et al. (2014)
Chemical reduction	Polyaniline/Au-Pd	2	100 µg mL ⁻¹ 25, 50, 75, 100, 125, 150 µg mL ⁻¹	Conventional bacteria	Zone of inhibition MIC	<i>Streptococcus sp.</i> : 21 ± 0.33 mm <i>Staphylococcus sp.</i> : 22 ± 0.35 mm <i>E. coli</i> : 25 ± 0.87 mm <i>Klebsiella sp.</i> : 21 ± 0.31 mm <i>E. coli</i> : 25–150 µg mL ⁻¹	Boomi and Prabu. (2013)
Deposition-precipitation method	Au/g-C ₃ N ₄	g-C ₃ N ₄ : 150 Au: 4	20 µg mL ⁻¹	Conventional bacteria; drug-resistant bacteria	Bacterial reduction (%)	Drug-resistant <i>E. coli</i> : 82% Drug-resistant <i>S. aureus</i> : 79%	Wang et al. (2017b)
Environmental redox method	Au-C	C: 200 Au: 10	5000 µg mL ⁻¹ 4000 µg mL ⁻¹	Conventional bacteria	Zone of inhibition MIC	5000 µg mL ⁻¹ <i>E. coli</i> : 15 mm <i>S. aureus</i> : 13 mm <i>C. albicans</i> : 10 mm 4000 µg mL ⁻¹ <i>E. coli</i> : 12 mm <i>S. aureus</i> : 0 mm <i>C. albicans</i> : 10 mm <i>E. coli</i> : 3200 µg mL ⁻¹	Gao et al. (2010)

MIC minimum inhibitory concentration, MDR multi-drug resistant, BSA bovine serum albumin, DAPT 4,6-diamino-2-pyrimidinethiol, MRSA methicillin-resistant *S. aureus*, Van vancomycin, g-C₃N₄ graphitic carbon nitride

et al. 2016). The experiment also found that the antibacterial mechanism of Au@ZnO is the generation of superoxide anion radicals under irradiation.

In addition to bimetallic nanocomposites, trimetallics have also been widely studied and applied. The addition of a third metal can add new dimensions and improve the properties of the materials. A group led by Yadava prepared a Au–Pt–Ag nanoscale fluid by green, microwave-assisted, continuous chemical reduction (Yadav et al. 2018). Trimetallic nanofluids show good antimicrobial activity. When the concentration of the composite was 15.625 mg/mL, the MIC for Gram-positive *S. aureus* was 31.25 mg/mL and that for *E. faecalis* was 15.625 mg/mL. For Gram-negative *E. coli*, *Salmonella typhi* and *Klebsiella* the MIC was 15.625 mg/mL. That was better antibacterial activity than bimetal and single metal nanofluids at lower concentration.

Gold nanoparticles modified with organic compounds

Given the antibacterial activity of some organic compounds, researchers have combined them with AuNPs seeking better antibacterial effects than those of gold nanoparticles alone. Indole derivatives, for example, can produce antibacterial compounds after certain chemical reaction, which confirms that they have antibacterial potential.

Zhao's experiments have shown that when AuNPs are modified with tryptophan and 5-aminopurine, the resulting Au–tryptophan and Au-5-aminopurine composites have excellent antibacterial activity against both bacteria and multi-drug-resistant (MDR) bacteria (Zhao et al. 2018). After 0.5 h of contact with either composite nanoparticle the elimination of viable MDR *E. coli* and polymyxin-resistant *K. pneumoniae* reached 99.9%. Even at the high bacterial concentration of 5×10^8 CFU/mL, more than 99.99% of polymyxin-resistant *K. pneumoniae* was inactivated after 4 h. Hareesh and his colleagues prepared a hexagonal gold–polycarbonate matrix of 110 nm particles by a radiation-assisted method (Hareesh et al. 2015). Their experiments showed good antibacterial action against Gram-positive and Gram-negative bacteria and showed the inhibitory effect of a dose of gamma radiation on the overall growth of bacteria. Two of the nanocomposites synthesized by Boomi's group through chemical methods were polyaniline/Ag–Au and polyaniline/Au–Pd (Boomi and Prabu. 2013; Boomi et al. 2014). Gold colloids did not show any inhibition zone for the four pathogens they studied, but when modified by polyaniline they showed inhibitory effects on all of the pathogens. They were also stable for several months.

Gold nanoparticles modified with carbon

One way to improve the antibacterial properties of nanomaterials is to synthesize gold nanoparticles on a supporting

material. This can effectively solve the problem of nanoparticle agglomeration. A group led by Gao synthesized a stable and dispersed Au/C shell-nucleus composite by a redox method (Gao et al. 2010). Au deposited on the surface of carbon spheres formed a gold shell 10 nm thick. Gold nanoparticles can inhibit microorganisms' growth better when dispersed on the surface of carbon spheres because they have more opportunities to contact bacteria.

Antibacterial mechanisms

As the problem of clinical bacteria resistance becomes more and more serious, single antibiotics have begun to lose bacteriostatic effectiveness. The hydrophilicity of some antibiotics causes them to cross through the water-filled channels of bacteria's membrane pore proteins. That leads to short residence time in the cells and weakens the bactericidal effect. The combination of nanogold and antibiotics has significantly improved antibacterial ability.

Gold nanoparticles sometimes break down cell walls in entering cells. They can thus help some antibiotics that cannot penetrate the cell wall barrier. The Au/AgNPs@Vancomycin synthesized by Lu's group in one step showed better antibacterial activity and weaker bacterial resistance than free vancomycin (Lu et al. 2017). The effect of vancomycin is to increase the adsorption of bacteria on Au/AgNPs@Vancomycin particles. Au/AgNPs@Vancomycin showed high antibacterial activity against Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria, with minimum inhibitory concentration (MIC) as low as 30 nmol mL^{-1} . 99% of the bacteria were killed within 5 h. Ag/AuNPs@Van2's cytotoxicity was lower. A group led by Khandelwal has synthesized nanoscale gold particles (AuNPs) labeled with cefradine (an antibiotic) (Khandelwal et al. 2015). A small amount of gentamycin sulfate combined with AuNPs can obtain more significant antibacterial properties than a single antibiotic (Fiori-Duarte et al. 2020; Zhou et al. 2020; Zou et al. 2020).

Experiments have shown that inhibition by AuNPs results from direct contact which induces cell wall rupture rather than by generating reactive oxygen species (ROS). Wang's laboratory synthesized Au@Ag-loaded Fe_3O_4 magnetic nanoparticles using a polyethyleneimine-assisted ligation method (Wang et al. 2016c). They showed good antibacterial activity against Gram-negative *E. coli* and Gram-positive bacteria *S. aureus*. In addition, streptomycin modification can significantly improve the antibacterial activity of Fe_3O_4 –Au@Ag nanoparticles. Streptomycin modification decreased the MIC by 25% for *E. coli* and 40% for *S. aureus*, indicating synergy between Fe_3O_4 –Au@Ag and antibiotics.

A group led by Coradeghini has tested the idea that AuNPs' uptake into cells increases with smaller particle size (Coradeghini et al. 2013). They found some effect of particle size on antibacterial mechanisms. Smaller nanoparticles can

enter cells. Larger ones cause cell lysis and death by acting on the surface. However, there is as yet no complete description of these mechanisms. The contact area of highly dispersed nanoparticles is larger, and their antibacterial activity is obvious.

Differences in surface modification also make a difference. The action modes of nanoparticles mainly include damaging the cytoderm, damaging cytomembranes and modifying the interior of bacterial cells. Alternatively, some nanoparticles modified with a photocatalytic metal rely on light excitation to generate free radicals for antibacterial purposes. The main antibacterial mechanisms of AuNPs are shown in Fig. 6.

Cytoderm damage

Cytoderm damage is results from the electrostatic attraction between positively charged nanoparticles and the negatively charged cytoderm, as indicated in Fig. 6a. Nanoparticles attached to the cytoderm can penetrate the cell by releasing copious ions to produce toxicity. Scanning electron microscopy has shown that AuNPs labeled with cefradine cause cell wall damage through direct physical contact. Moreover, the measurement of ROS through fluorescent probes ruled out the possibility of ROS leading to the observed loss of cell viability (Khandelwal et al. 2015). Experiments have shown that gold nanorods causes membrane damage through

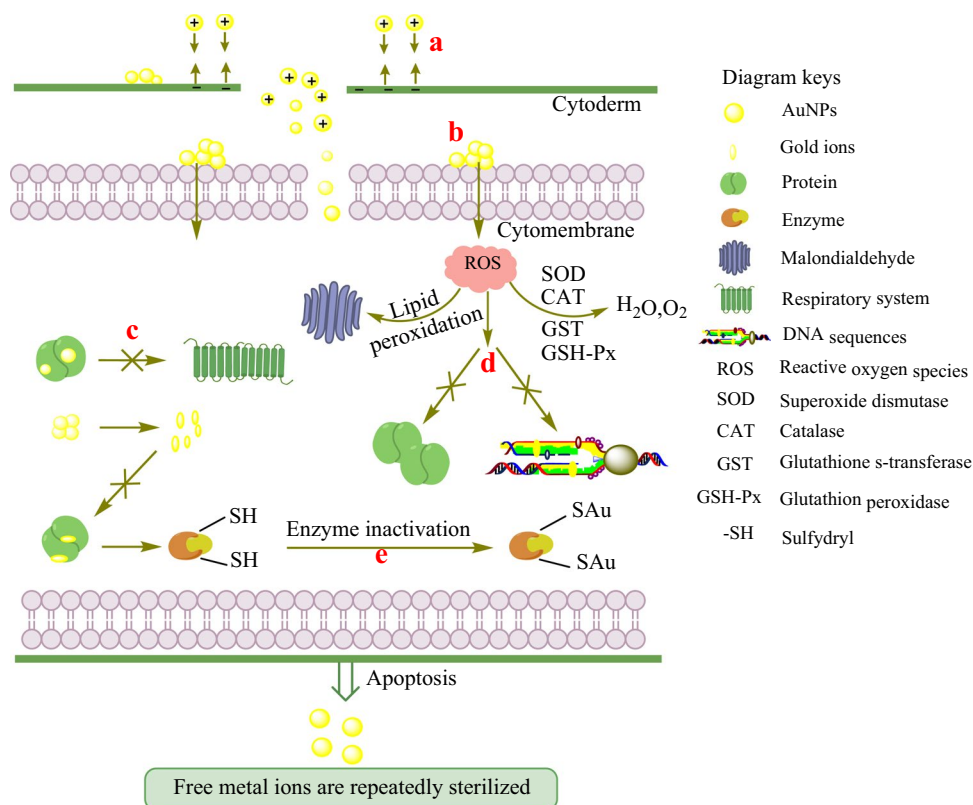
electrostatic attraction between the gold and the cytoderm, which eventually leading to cell death (Arockia Jency et al. 2020; Lanh et al. 2015).

Interestingly, many studies have found that gold nanoparticles have different effects on Gram-negative and Gram-positive bacteria. Gao's group dispersed gold nanoparticles uniformly on the surface of carbon spheres. Such Au/C core-shell nanomaterials proved more effective in killing Gram-negative than Gram-positive bacteria. The MIC for *E. coli* was 3200 µg/mL. Only when the concentration of the composite reached 5000 µg/mL did it show good antibacterial ability against Gram-positive bacteria (Gao et al. 2010). This may be due to differences in the cytoderm. Gram-positive bacteria contain a large amount of peptidoglycan and have a thick cytoderm (20–80 nm). Gram-negative bacteria only have a thin layer of peptidoglycan, and the cytoderm is thin (10 nm). The metal ions released by the nanoparticles can more easily invade the thin-walled Gram-negative bacteria. But not all the research results agree. Therefore, in addition to the influence of the cell wall structure, there are other factors.

Cytomembrane damage

Biofilms are extracellular molecules wrapped around the surface of bacteria. Their high resistance is one thing that makes bacterial diseases difficult to cure. Bacteria produce

Fig. 6 Possible antibacterial mechanisms of gold nanoparticles (AuNPs). **a** Positively-charged nanoparticles electrostatically adsorbed to the negatively-charged cytoderm; **b** the accumulation of nanoparticles disrupts the intra-cellular balance, resulting in reactive oxygen species (ROS) oxidation of biofilms and oxidative stress; **c** the combination of gold ions and proteins destroys the microbes' respiratory systems and electron transport chains; **d** the ROS damage cellular DNA and proteins; **e** metal ions react with sulfhydryl groups to destroy cellular synthetase activity



ROS when exposed to gold nanoparticles. Because the cell membrane is negatively charged, it is not easily penetrated by negatively charged reactive oxygen species. However, H_2O_2 can penetrate the cell membrane and induce cell membrane damage (Padmavathy and Vijayaraghavan 2008).

Another way for nanoparticles to play an antibacterial role is to break up the cytomembrane and let the cell contents flow out. The adsorption of gold nanoparticles on the membrane can cause the necessary membrane damage (Liu et al. 2006) as indicated in Fig. 6b. The TEM results published by Zhao show that the cytomembranes of bacteria treated with Au–tryptophan and Au–5-aminopurine nanocomposites were broken, while the cytomembranes of untreated bacteria were intact (Zhao et al. 2018). This suggests that the antibacterial mechanism of gold nanocomposites is the destruction of cell membrane.

Photothermal therapy uses near-infrared radiation to induce AuNPs to produce surface plasmon resonance, which destroys the cytomembrane structure and kills bacteria by local heating (Aksoy et al. 2020; Hsiao et al. 2015). Zhang's group synthesized a series of gold composites with modified titanium oxide using a hot sol method (Zhang et al. 2016). Experiments show that surface plasmon resonance produced by AuNPs can significantly improve the visible light absorption characteristics of TiO_2 . The 1% Au– TiO_2 composite was able to kill *E. coli* in the dark. After 5 h of treatment, the survival rate of *E. coli* was 73.3%. The cell death may have been due to electrons generated by the Au nanoparticles on the cytomembrane (Li et al. 2014c).

Gold ion release

The antibacterial activity of gold nanoparticles is partly due to the release of gold ions (Wang et al. 2014). The higher the added concentration of gold nanoparticles, the more gold ions will be released, and the better the antibacterial effect will be (Tamayo et al. 2014). Smaller nanoparticles release Au^+ faster due to their greater specific surface area. When bacteria are exposed to the nanoparticles, the Au^+ released is evenly distributed around the bacteria. They penetrate cell walls and enter the cells where they can react with thiol groups to form Au–thiol groups. Thiol groups on cysteine can cause protein coagulation. Disulfide bridging between cysteine residues is involved in protein folding (Slavin et al. 2017). The combination of gold ions and cysteine also disrupts the microbes' respiration and electron transport systems, as indicated in Fig. 6c. There are also mercaptan groups in the cell wall synthetase pathway. Binding sulfhydryl groups destroys synthase activity, halting cell division and proliferation and causing cell death. The process is represented in Fig. 6e.

Internal effects on bacterial cells

Active oxygen can be oxygen-containing free radicals or forms of peroxide without free radicals. It is formed in basic metabolism. Reactive oxygen maintained at an appropriate level has a positive effect on cells. However, the level of reactive oxygen species rises significantly when cells face external stimuli. Excess reactive oxygen species can then have negative effects. AuNPs in contact with bacteria generate O_2^- , H_2O_2 , $\text{HO}_2\cdot$ and $\cdot\text{OH}$. These ROS cause oxidative stress which leads to lipid peroxidation in the cytomembrane. That is, ROS react with macromolecular substances such as phospholipids, enzymes and nucleic acids of the cytomembrane to form lipid peroxidation products. That increases the cytomembrane's permeability, which eventually leads to changes in cell structure and function.

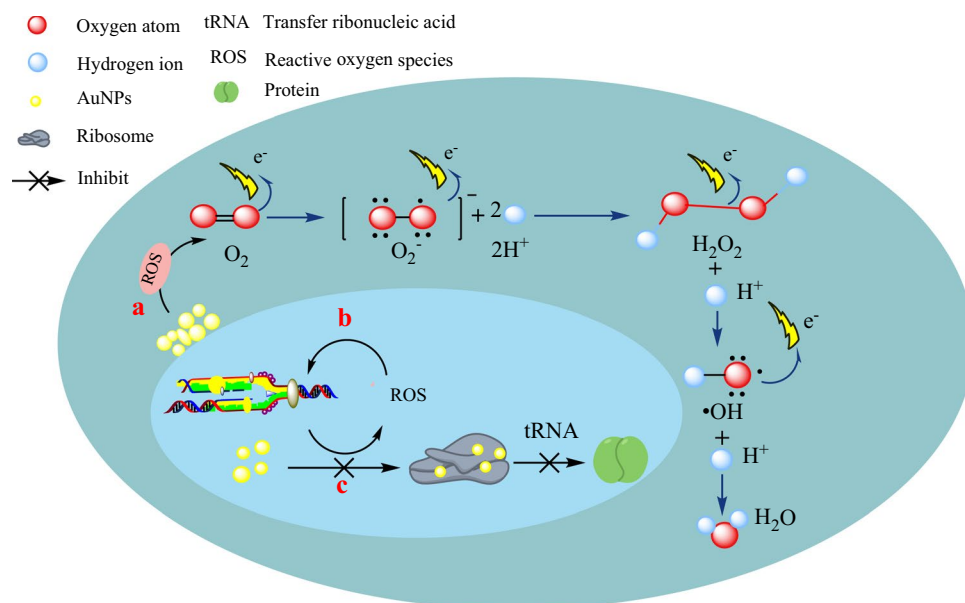
In addition, AuNPs can cause bacterial death by causing ROS production within cells, resulting in protein aggregation and DNA destruction as Fig. 6d illustrates (Wang et al. 2016b). The mechanisms of action of ROS are shown in Fig. 7 (Slavin et al. 2017). He and his colleagues synthesized ZnO/Au hybrid nanostructures using a photoreduction method and used electrons photoinduced by ZnO to reduce Au^{3+} on the ZnO surface (He et al. 2014). Gold was deposited on the ZnO surface, which caused $\cdot\text{OH}$, O_2^- and H_2O_2 to be generated by light excitation. This is the main mechanism of its antibacterial ability. The antibacterial efficiency of ZnO/Au composite nanomaterials against *E. coli* is three times that of ZnO alone. In addition to lipid peroxidation, oxidative stress can also cause damage in the form of DNA strand breaks and base modifications, as indicated in Fig. 6d. Gold nanoparticles that enter the cell affect protein synthesis by inhibiting the binding of ribosomal subunits to tRNA.

In practical applications, gold nanoparticles must not only have excellent antibacterial ability, but also maintain low toxicity to normal cells. AuNPs have good biocompatibility (Norouzi 2020). Small AuNPs may enter normal cells with nutrients. It is worth noting that the decomposition of foreign substances in the lysosomes of normal cells can partially antagonize the adverse effects of AuNPs. Lysosomes are not found in bacteria. In other words, AuNPs can exert their antibacterial effect without damaging normal cells.

Conclusion

There are two main approaches useful for preparing functionalized nanoscale gold composites. One is to optimize the material's particle size, morphology and dispersibility by controlling the reaction conditions for the best performance. The other is to bolster the nanomaterial's properties with ligands. The preparation of nanoscale gold mainly relies on the seeded growth method, green synthesis with

Fig. 7 Mechanisms of reactive oxygen species (ROS). **a** Bacteria exposed to gold nanoparticles (AuNPs) produce ROS and induce oxidative stress; **b** ROS inhibit DNA replication; **c** inhibition of ribosome function leads to ROS production



plant extracts or chemical reduction. The resulting material can then be functionalized. The antibacterial properties of nanoscale gold particles (AuNPs) are closely related to the particle size, dispersibility and surface modification of the nanoparticles. AuNPs mainly cause cell lysis and death by electrostatic adsorption on the bacterial surface, membrane damage and reactive oxygen species (ROS) damage to proteins and DNA. AuNPs have good biocompatibility and no cytotoxicity.

At present, most of the antibacterial studies with AuNPs have been with conventional bacteria. There have been relatively few studies with multi-drug-resistant bacteria. That is an essential direction for future research. Antibacterial activity is expressed in terms of minimum inhibitory concentration (MIC), zone of inhibition, bacteria reduction, survival percentage and the rate of bacteria inactivation. Because of the different units, it is difficult to make objective comparisons among different studies. This is one of many aspects of nanoscience that need to be standardized. In addition, combining theoretical research findings with clinical application is a difficult point. There are still no firm conclusions for many issues. Among them are the site and specificity of nanoparticles' action on the cytomembrane and their transmembrane action. Whether AuNPs still have good long-term biocompatibility in vivo also requires further verification.

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was written by Xiao Gu and Fengxia Han, and other authors (Huayun Xu, Bo Chen, Xuejun Pan) critically revised the work. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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