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REVIEW ARTICLE

Gold nanoparticle surface engineering strategies and their applications in biomedicine and diagnostics

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Abstract

Gold nanoparticles (AuNPs) have found a wide range of biomedical and environmental monitoring applications (viz. drug delivery, diagnostics, biosensing, bio-imaging, theranostics, and hazardous chemical sensing) due to their excellent optoelectronic and enhanced physico-chemical properties. The modulation of these properties is done by functionalizing them with the synthesized AuNPs with polymers, surfactants, ligands, drugs, proteins, peptides, or oligonucleotides for attaining the target specificity, selectivity and sensitivity for their various applications in diagnostics, prognostics, and therapeutics. This review intends to highlight the contribution of such AuNPs in state-of-the-art ventures of diverse biomedical applications. Therefore, a brief discussion on the synthesis of AuNPs has been summarized prior to comprehensive detailing of their surface modification strategies and the applications. Here in, we have discussed various ways of AuNPs functionalization including thiol, phosphene, amine, polymer and silica mediated passivation strategies. Thereafter, the implications of these passivated AuNPs in sensing, surface-enhanced Raman spectroscopy (SERS), bioimaging, drug delivery, and theranostics have been extensively discussed with the a number of illustrations.

Keywords Gold nanoparticles · Synthesis approaches · Surface functionalization strategies · Biomedical applications

Introduction

Advancement in nanomaterial researches have shown a great impact in clinical diagnostics, therapeutics, and energy generations (Chandra et al. 2010; Kumar et al. 2018; Mahato et al. 2018a; Prasad et al. 2016). The common properties shown by nanoparticles (NPs) are (1) high surface-to-volume ratio, (2) ease of functionalization enabling specific target-binding properties, (3) tuneable optoelectronic properties, and (4) high robustness of the NPs (Baranwal et al. 2016), which enables them in various biomedical applications. In recent years, NPs of various materials *viz*. metals, non-oxide ceramics, metal oxides, silicates, polymers, biopolymers, and carbon have been used for such applications (He et al. 2000; Baranwal et al. 2018a). Noble metal NPs especially gold (Au) and silver (Ag) have fascinated researchers for decades and are being extensively used due to their excellent compatibility towards the biological systems (Baranwal et al. 2018b; Elahi et al. 2018). Among all, AuNPs are considered as a most important candidate due to its chemical inertness, environmentally benign nature, and biocompatibility when functionalized with appropriate

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ligand/group of ligands (Blanco et al. 2015; Sahoo et al. 2017). The first scientific note on AuNPs synthesis was reported by Michael Faraday in the early nineteenth century where the synthesis was done using chloroauric acid and phosphorous as the reducing agent (Faraday 1857). In this context, Turkevich and co-workers delivered the major breakthrough by demonstrating the synthetic mechanism of AuNPs formation in colloidal systems (Turkevich et al. 1951; Daniel and Astruc 2004). In recent years, numerous methods of AuNPs synthesis along with its numerous applications have been reported (Chen et al. 2018; Strozyk et al. 2018), however, the whole essence of these advancements was driven for obtaining the facile synthetic process, characterization, functionalization, and applications of these uniquely fabricated AuNPs (Mandal et al. 2018; Chandra et al. 2013b). Chemically, elemental gold ($[Xe]4f^{14}5d^{10}6s^{1}$) contains electrons that can move freely throughout the metal and exhibits three oxidation states including Au [0], aurous (+1 Au [I]), and auric (+3 Au [III]) form. The availability of free electrons at the atomic surface and multiple oxidation states of metal facilitates the formation of stable nanostructures. Depending on the synthetic procedure, nature of solvent, solution pH, and surface passivating agents, these nanostructures are obtained of varied sizes and shapes. Due to its immense capabilities of exhibiting varied tunable optical, fluorescence, SPR, and magnetic properties, it has found a wide range of clinical and biomedical applications (Biju 2014). The other factors including greater stability, biocompatibility, selectivity, and lesser toxicity in the biological environment have led AuNPs for reliable commercial usage (Kumar et al. 2018). Surface modifications of AuNPs play a crucial role in achieving the enhanced properties for various biomedical applications. So far, various molecules of chemical and biochemical origin have been used to obtain such functionalized AuNPs by tuning the physicochemical behavior of AuNPs, i.e., the surface charges, ligand-binding ability, etc. These modifications of AuNPs commonly done using thiols, amines, phosphines, silica, carboxy-terminated groups, etc., eventually help to conjugate a number of biomolecules (Alex and Tiwari 2015).

Methodologically, these passivating processes follow either covalent-based modifications or non-covalent interactions. A strong Au–S covalent interaction has been reported using organothiols, disulfides, and cysteine groups, whereas the non-covalent interaction has been achieved by physiosorption and electrostatic interactions of surface-ionized ligands (Alex and Tiwari 2015). Based on their reaction involved in the covalent process, these modifications have been categorized under the direct and indirect covalent coupling. The direct coupling rely on the attachment of the ligand on the AuNPs surface, however, when the direct binding is not favorable, the linking process is done with the shell of stabilizing molecules encapsulating the AuNPs using various bio-conjugation techniques viz. carbodiimide, biotin-streptavidin, and silane coupling reactions (Craig et al. 2010). So far, the functionalized AuNPs have been exploited for a wide range of biomedical applications, not only in research and development sector but also in various commercially viable point of care systems viz. cyto-sensors (Koh et al. 2011), immuno-sensors (Noh et al. 2012), drug delivery (Baranwal et al. 2018b), cancer imaging (Wu et al. 2015), apta-sensing (Chandra et al. 2013a), and most advanced theranostics devices (Song et al. 2016). In this context, theranostic devices are one of the modern advents in biomedical devices, which delivers the precise sensing and accurate therapeutic effect synergistically.

The intention of this review is to summarize the extensively used various strategies for AuNPs synthesis and functionalization followed by its biomedical applications. For that, we have provided a brief introduction to the AuNPs synthesis before discussing its functionalization strategies to put wider insight to the readers. Thereafter, we have discussed diverse kind of passivating strategies used for AuNPs, where we have covered majorly employed techniques *viz*. thiol, amine, polymer, and silica-based modification. In the next section, we have described the application of such passivated AuNPs in various domains *viz*. biosensing, bioimaging, therapeutics, drug delivery, and most advent theranostics.

Synthesis of AuNPs

Methodologically, the synthesis of AuNPs follows two types of approaches, including "top-down" (physical manipulations) and "bottom-up" (chemical transformations) approaches (Mandal et al. 2018; Teimouri et al. 2018; Abalde-Cela et al. 2018; Elahi et al. 2018; Catherine and Olivier 2017). In the top-down strategy, bulk gold is gradually eroded by physicochemical mechanisms until the desired size and shape is achieved. For example, gold clusters have been made from the bulk using attrition and pyrolysis. In attrition-based techniques, the bulk gold have been grounded into macro- or micro-scale particles by reducing the size, however, these size reducing mechanisms rarely produce a homogenous range of NPs. In pyrolysis, the bulk gold is heated to atoms and those atoms reform to gold clusters *viz*. physical vapor deposition and chemical vapor deposition. In these processes, the bulk gold is thermally heated to atoms under an inert atmosphere and the cooled metal atoms are deposited on a cold finger to form metal clusters. When the process is finished, the metal clusters can be collected from the cold finger (Schmid 2005). The limitations associated with top-down strategies are the requirement of stronger interactions between metal and capping ligands and

the techniques used in this strategy involve expensive cumbersome instruments.

For the biomedical applications, NPs synthesized by the bottom-up approaches are considered to be more suitable, due to their relatively uniform shapes and sizes (Baranwal et al. 2016). It involves the reduction of Au^{+3} salts in the presence of various reducing and stabilizing agents, where Au atoms form clusters and subsequently to the particles by undergoing the nucleation process (Turkevich et al. 1951; Yeh et al. 2012). In this process, the stabilizing agent passivates the nanoparticle's surface and thereby prevents further aggregation. Commonly, there are two types of passivating agents used for stabilizing the AuNPs formed in bottom-up approaches, which are either from chemicals or extracted biochemical (Baranwal et al. 2016). There are a number of methods been reported for AuNPs synthesis using such chemicals or extracted bio-chemicals. These reducing biochemicals are commonly obtained from various vegetation sources including plant, algae, bacteria, and fungi (Shankar et al. 2003a, b; Dhas et al. 2012; Nair and Pradeep 2002). Since, the chemical-based AuNPs syntheses were achieved with well-defined compositions of pure reducing agents found a great advantage of scaling up of the synthetic process, while the extracted reducing soup from the biological sources facilitates the complex synthetic process that might lead to complex downstream purification and lower scaling capabilities (Sau and Rogach 2012). Due to easy fabrication and facile nano-manipulations, the chemically synthesized AuNPs are widely used in various application including biosensing, bio-imaging and nano-medicine (Chandra et al. 2010, 2012). Figure 1 shows a schematic representation of the bottom-up and top-down synthesis strategies.

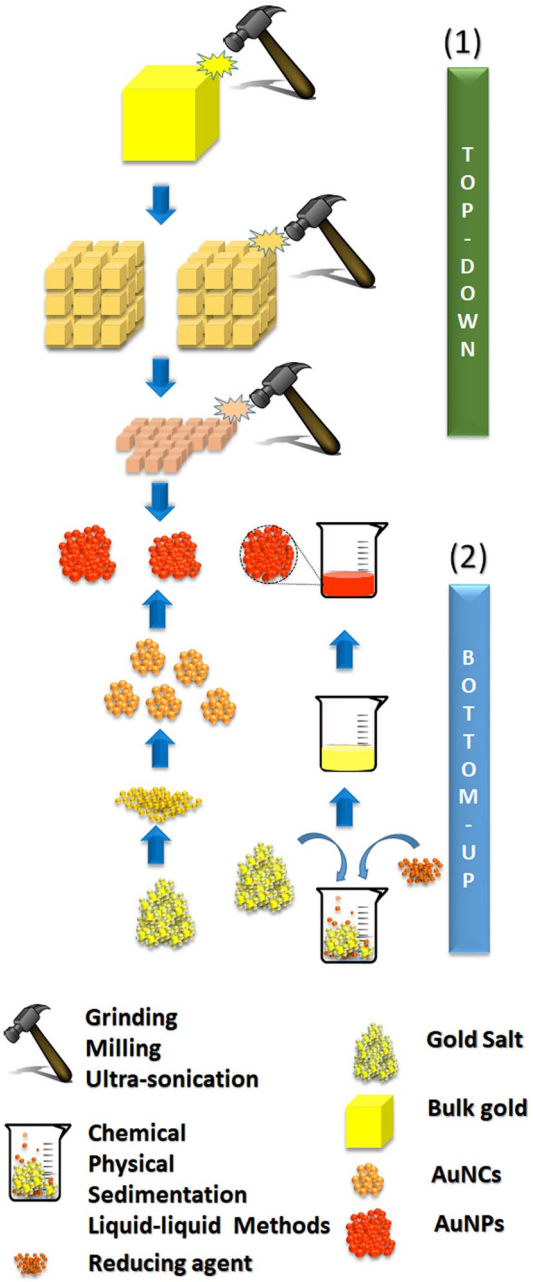

Fig. 1 Schematic representation of NP syntheses using **(1)** top-down and **(2)** bottom up approaches

Surface modification strategies

Surface modification using sulfur-containing ligands

Direct conjugation to form thiol-protected AuNPs

Surface modifications of AuNPs involve the binding of linker molecule onto the surface, where thiol-based coupling have extensively been employed. These alterations provide the control over reactivity and induction of hydrophobicity/hydrophilicity to the NPs. These NPs are obtained by following the direct conjugation of thiol containing molecules during the synthesis of AuNPs (shown in Fig. 2). In an example, synthetic process follows the dissolution of chloroauric salts ($HAuCl_4$) to obtain $AuCl^{4-}$ ions in water followed by phase extraction of $AuCl^{4-}$ ions at tetraoctyl ammonium bromide (TOAB) dissolved in toluene. Thereafter, the process was followed by the treatment of reducing agent (sodium borohydride; $NaBH_4$) and 1-dodecanethiol in the solution. The rapid color change (orange to deep brown) of the solution in presence of 1-dodecanethiol authenticates the formation of thiol-capped AuNPs. In final steps, the thiolated AuNPs were purified following the phase extraction and thorough washing of AuNPs. The overall reaction has been summarized in Eqs. (1) and (2):

$$AuCl_4^-(aq) + N(C_8H_{17})_4^+(C_6H_5Me) \rightarrow N(C_8H_{17})_4^+AuCl_4^-(C_6H_5Me) , \quad (1)$$

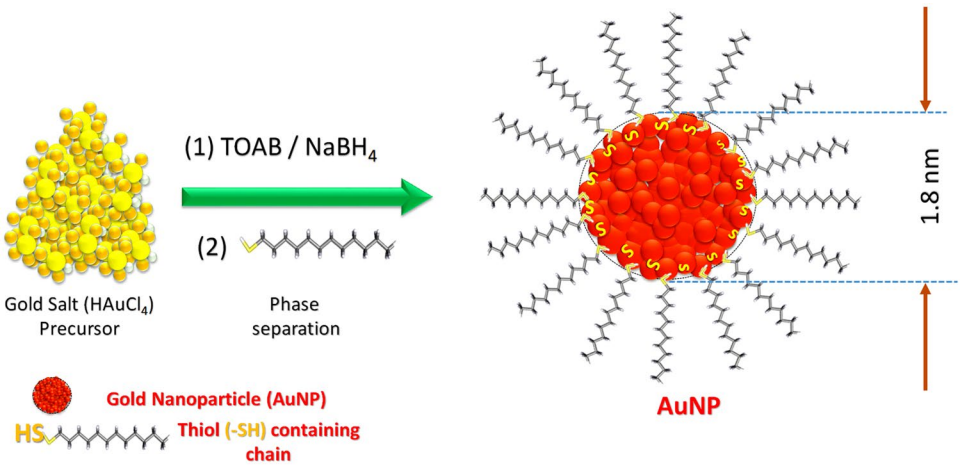

Fig. 2 The pictorial representation of thiol-stabilized AuNPs synthesis based on the phase extraction process using **(1)** tetraoctylammonium bromide [TOAB; $(C_8H_{17})_4NBr$] followed by the reduction with sodium borohydrite ($NaBH_4$) **(2)** Particles are capped using dodecane thiol ($C1_2H_{25}SH$)

$$m\mathrm{AuCl_4}^{-}\left(\mathrm{C_6H_5Me}\right) + n\mathrm{Cl_2H_{25}SH}\left(\mathrm{C_6H_5Me}\right) + 3me^{-} \rightarrow 4m\mathrm{Cl}^{-}(aq) + \left(\mathrm{Au}_m\right)\left(\mathrm{Cl_2H_{25}SH}\right)_n. \quad (2)$$

In the above case, mainly AuNPs of cuboctahedral and icosahedral structures shape were synthesized in size range of 2–8 nm with a dispersion of about 4–6%, however, the particle's shapes and sizes can be tuned by altering the reaction conditions; such as, gold/thiol molar ratio, temperature, and reduction rates. For instance, the fast reductant addition and low solution temperature have been reported with the smaller and monodisperse particles. In addition, the tuning of size has also been achieved by introducing a sterically bulky group for immediate quenching of reaction (Templeton et al. 2000). In addition to these, the optimization of reducing temperature and rate of injection of reductant have also been reported to alter the size and dispersity index of AuNPs (Schaaff and Whetten 2000). To achieve thiol-coated AuNPs, a number of methods have been employed to synthesize, where Brust–Schiffrin procedure is well known for monolayer-protected clusters (MPCs) formation, wherein further steps, the purification was performed using TOAB to obtain high yield (Waters et al. 2003). Apart from these, catalyst-less synthesis of MPCs has also been reported without trace ionic impurities by coupling the two different single-phase steps. For instance, thiol-derivatized AuNPs in a two-phase liquid–liquid system was synthesized by simultaneous reduction of the gold salt in the presence of passivating ligand using a water/methanol solution. This method was originally demonstrated with 4-mercaptophenol as capping agent (Brust et al. 1995) and is widely used for the incorporation of water-soluble ligands (Chen and Kimura 1999; Templeton et al. 1999). In another single-phase synthetic approach (Rowe method), tetrahydrofuran (THF) is used as the solvent which provides several advantages including compatibility for a wide range of ligands. The usage of strong reducing agents [lithium triethyl borohydride (super-hydride)] in this method has increased the efficiency by multiple folds than Brust method due to its capability of reducing various functional groups including esters and amides (Brown et al. 1980), where the two-phase Brust method limits.

In addition to this, a number of surface modifications have also been reported by translating the double phase synthesis into a single-phase system (Kanaras et al. 2002; Zheng et al. 2004). For instance, the tiopronin monolayer-protected AuNPs were obtained in soluble gold clusters with the average core size of 1.8 nm (Templeton et al. 1999). Similarly, the relatively smaller and thermally stable AuNPs have also been synthesized using arenethiol and alkanethiol as a passivating layer (Chen and Kimura 1999). Not only smaller sizes, but also larger sized thiol-stabilized water-soluble AuNPs were obtained using alkyl thiosulphates as precursors (Lohse et al. 2010). In addition to these, various thiol-based approaches have been reported for the AuNPs surface modification including thymine self-assembled monolayer (Zhou et al. 2007), hexadecyl aniline (Ascencio et al. 2000), super hydride (Yee et al. 1999), organometallic reagents, (2-propylmagnesium bromide) (Sugie et al. 2009), 9-borabicyclononane (Sardar and Shumaker-Parry 2009), and glutathione (Negishi et al. 2004) based thiol-passivated AuNPs.

Substitution/secondary modification to form mixed-monolayer AuNPs

For the first time, Giersig and Mulvaney reported Mixed-monolayer mediated modification of AuNPs in 1993, where the AuNPs were stabilized using alkanethiols. This stabilization was introduced by mixing end-group functionalized organothiols (ω-functionalized organothiols) with pre-synthesized AuNPs in the presence of surfactants. Due to the soft character of gold and sulfur, thiol groups strongly bind to the gold through covalent interaction (Giersig and Mulvaney 1993) and hence the formed NPs

show excellent stability and can be stored for years (Brust et al. 1995). Thus, to modify the surface of AuNPs, place-exchange methods are profoundly used where the substitution of existing thiol ligands from additive thiols are introduced. Templeton et al. and Hostetler et al. have shown method for the substitution of anchored thiol with the free thiol ligands (Hostetler et al. 1999; Templeton et al. 2000). The introduction of two or more functional ligands has also been reported for the synthesis of mixed-monolayer-protected AuNPs for synergistic applications. For example, hybrid AuNPs have been prepared using thiol-terminated ligands containing organic/inorganic dyes (Walter et al. 2002), smart polymers (Martin 1996), biomolecules (Giljohann et al. 2010), and drug molecules (Ghosh et al. 2008). These ligands on the surface of AuNPs interact amongst each other creating a rigid monolayer (Jadzinsky et al. 2007) which exhibits a certain level of intra-monolayer mobility as an optimal interaction with the analytes (Boal and Rotello 2000). Under the appropriate conditions, these ligands show intermolecular mobility by hopping between the NPs (Zachary and Chechik 2007) due to the effects of temperature and monolayer packing (Ionita et al. 2008). In general, the core of AuNPs contain hydrophobic groups and the secondary surface modifications with hydrophilic groups (viz. hydroxyl or carboxy moieties) helps to improve the dispersion of AuNPs preventing their aggregation. So far, a number of strategies have been reported following mixed-monolayer-based passivating approaches including the chemical coupling (Liu et al. 1998), polymerization (Mandal et al. 2002), electrostatic interaction (Chen et al. 2008), and selective intermolecular interaction (Giljohann et al. 2010; Braun et al. 2009). Among all, chemical coupling and polymerization are the most widely used methods, where the functionalization of AuNPs using carboxylic acid terminated was mostly used. In one of such examples, thiol ligands have also been used that forms amide linkage with linker molecules via. *N*-Ethyl-*N*-(3 dimethylaminopropyl)-carbodiimide coupling (Kamra et al. 2016). Apart from these, NPs with hydroxyl groups on their surface have also been reported to generate various functionalities by esterification reaction in presence of acyl moieties (Fig. 3) (Yoo et al. 2009).

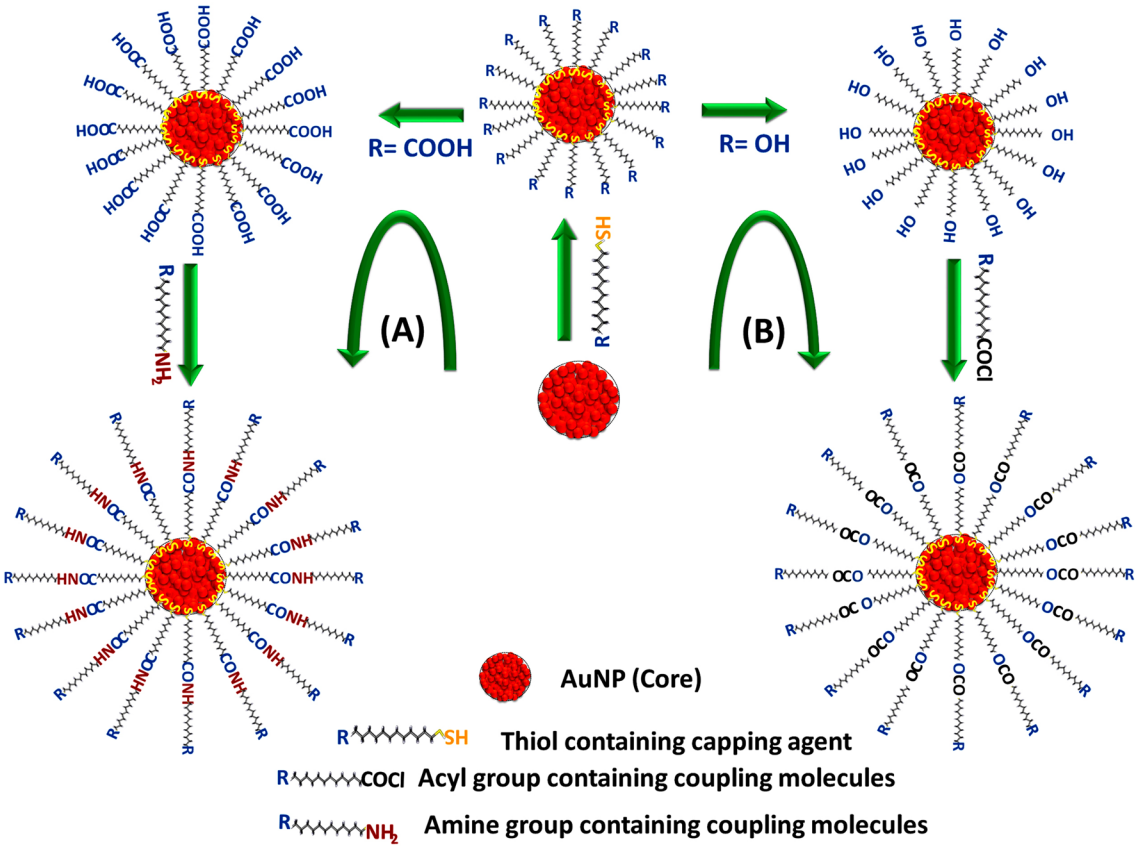

Fig. 3 Schematic representation of different types of secondary modification approaches for mixed-monolayer-passivated AuNP functionalization, **(a)** carbodiimide coupling at carboxylic end thiolated AuNPs **(b)** hydroxyl end thiol-stabilized AuNPs using RCOCl coupling reaction

Modification using other sulfur ligands

Sulfur-containing ligands viz. xanthates (Tzhayik et al. 2002), disulfides (Manna et al. 2003), di- and trithiols (Felidj et al. 2003), thioacetates, dithiocarbamates, trithiolates, thiolic acid, and resorcinarenetetrathiols (Balasubramanian et al. 2002) have also been used to functionalize AuNPs surface. In one such example, small-sized AuNPs (diameter 1.5 nm) have been prepared using a four-chained disulfide organic molecule. Since, the thiol moieties give better stabilization to AuNPs, these are most commonly used over other ligands for passivation. In addition, thio-ether- stabilized AuNPs have also been reported for AuNP surface functionalization, which shows relatively weaker passivating capacity (Shelley et al. 2002). Thus, to circumvent the limitations associated with the monomeric layer, poly-thio-ether passivating agents were used to stabilize the AuNPs (Li et al. 2001). Furthermore, metal-binding strengths between thiols and thio-ethers differ and hence alter the molecular arrangements, which contain multidentate thio-ethers that eventually lead to the unique morphologies and also allow the chemical reversibility. For instance, the tetradentate thio-ethers have been used to form reversible AuNP assembly (Maye et al. 2002). In another example, Sun et al. have described the synthesis of polycyclodextrin hollow gold spheres through oxidation-mediated thiol-stabilized AuNPs using iodine, resulting in decomposition to gold iodide with disulfide formation (Sun et al. 2001). However, the dispersion of these particles is major concerns especially in an organic solvent, thus to obtain improved dispersible particles, resorcinarene tetrathiol has been employed as a passivating agent, which is reported to yield mid-sized AuNPs (16–87 nm) (Yamamoto and Nakamoto 2003).

Surface modification using phosphine

The surface of AuNPs has also been stabilized and modified using phosphine, which is reported to act as an excellent precursor for functionalization with well-defined metallic cores (Weare et al. 2000). These functionalized particles have been used not only for catalysis (Schmid 1992) but also has been employed as the backbone for nanoscale electronic devices (Weare et al. 2000). Commonly, the approaches for synthesizing the phosphine- based AuNPs are carried out by the reduction of $HAuCl_4$ followed by the treatment of phosphine derivatives for stabilizing the nanostructure such as $PPh_2(C_6H_4SO_3Na\text{–}m)$ or $P(C_6H_4SO_3Na\text{–}m)_3$ (Schmid et al. 1996). In a report, the phosphine-mediated AuNPs were obtained, where the chloroaurate ($AuCl^{4-}$) ions have been relocated after the reduction in aqueous $NaBH_4$ to the organic phase (toluene) containing PPh_3 (Weare et al. 2000). These uniquely synthesized NPs not only show the greater stability when stored in cold and dry conditions but also allow excellent surface functionalization. The process has also been tuned for larger particles synthesis by adjusting the important parameters of reaction time and temperature. In another strategy, AuNPs have been synthesized by following the Hutchison's procedure where the rapid exchange of phosphine derivative of the different genre was employed, i.e., capping ligand and dissociated phosphines occur in dichloromethane at room temperature (Petroski et al. 2004). NPs from Hutchison's preparation can also serve as the versatile AuNP precursors as the functionalization can be achieved with a wide range of ligands from ligand-exchange reactions to yield a diverse library of functional "nano-building blocks", which can eventually lead to the unique nanostructures.

Surface modification using amine

Similar to the previously discussed strategies, there are a number of methods reported for the AuNPs surface functionalization. For this, Brust method is commonly adopted to modify the surface of NPs, where the present stabilizing thiol moieties are substituted by amine ligands. The major advantage of amine-capped AuNPs is that the surface chemistry of NPs can easily be probed by a variety of spectroscopic studies. Initially, the hydroxylamine has been used as a reducing agent for amine-capped AuNPs synthesis (Graf and van Blaaderen 2002). This paved the path towards extensive use of organic amines in a number of metal NPs, especially for AuNPs, due to their affinity for nitrogen. Amine-mediated synthesis of hydrophobic AuNPs has also been reported by Leff and co-workers using n-alkylamines (primary amines) (Leff et al. 1996). Similarly, aminomethyl pyrene (Thomas and Kamat 2000) and benzylamine (Thomas et al. 2002) have been reported to be used as stabilizing agents to obtain amine stabilized AuNPs. For simplifying the synthesis process, a direct one-pot synthesis of amine-stabilized AuNPs using 3-trimethoxysilylpropyldiethylenetriamine has also been reported (Zhu et al. 2005). In addition to this, Aslam et al. demonstrated a one-step synthesis of oleylamine-capped water-soluble AuNPs (Aslam et al. 2004). Furthermore, a higher ratio of gold to amine has been used for the formation of products with mixed ligand shell, which suggests the ratio of the gold salt and amine ligands defines the dispersity index. Newmen et al. have reported an interesting study in this context, where the different ratios have tested for the AuNPs syntheses and found that in the ratio of 10:1(gold to amines) yields monodisperse nanoparticle, while the further lowering of amine ligands leads to the synthesis of polydispersed AuNPs. In addition to these, a variety of other amino compounds have also been employed to obtain amine-capped AuNPs including aromatic amines (Newman and Blanchard 2006), diamines (Selvakannan et al. 2004), tetraoctylammonium (Isaacs et al.

2005), laurylamine (Kumar et al. 2003), porphyrins (Kotiaho et al. 2010), and hyperbranched polyethylenimine (Duan and Nie 2007).

Apart from these, amino acids are also used for the amine passivation of AuNPs as these are capable of forming protective layers and the assembly of chloroaurate ions forming NPs. Functional groups of amino acids, viz. −SH and $-NH_2$ possess high affinity for gold (Choudhary et al. 2016), thus provides the greater stability to the NPs. The physicochemical properties of the side groups present in the amino acids, such as polarity and hydrophilicity influence the reduction, stabilization, and conversion of gold ions (Au^{3+}) to NPs (Huang et al. 2006b). So far, several amino acids have been reported for surface modification including tryptophan, lysine, aspartic acid (Shao et al. 2004), cysteine (Ma and Han 2008), and glutamic acid (Wangoo et al. 2008). In a report published by Selvakannan and co-workers, the synthesis and functionalization of water-soluble AuNPs have been mediated by amino acid lysine (Selvakannan et al. 2004). These lysine-capped aqueous AuNPs are electrostatically stabilized in solution and show excellent water-dispersibility. However, the AuNPs obtained from amine capped methods show pH dependent properties, due to which the particles aggregates to large superstructure on the fluctuation of pH.

Surface modification using polymers

The polymers have also been used for capping the metallic NPs to provide greater stability. Initial attempt on polymer-stabilized AuNPs has been taken by Helcher in the presence of a polysaccharide in 1718, however, due to limited characterization availability, these were not properly and scientifically analyzed (Rac et al. 2014). Polymer-stabilized AuNPs have many advantages, which include longer stability, high surface density and ability to adjust solubility (Chandra et al. 2012; Zhu et al. 2012a; Chandra 2016). Few commonly used polymers for stabilization are: poly(*N*-vinylpyrrolidone) (PVP), poly(ethylene glycol) (PEG), poly(4-vinylpyridine), poly(vinyl alcohol) (PVA), poly-(vinyl methyl ether), chitosan, polyethyleneimine (PEI), poly(diallyl dimethyl ammonium chloride) (PDDA), polystyrene-block polymers, poly(methyl methacrylate) (PMMA), poly(dG)-poly(dC), and poly(N-isopropylacrylamide) (Mandal et al. 2002; Yilmaz and Suzer 2010). The adopted strategies for polymer stabilization follow (1) grafting from, (2) grafting to, and (3) post-synthetic modification approaches. A simple schematic representation of these methods has been shown in Fig. 4.

Grafting-from technique

The "grafting from" approach involves growing polymeric chains from scaffolds attached to the surface of AuNPs (Huo and Worden 2007; Shan and Tenhu 2007). Commonly, alkyl-thiol-passivated AuNPs are used as a precursor for capping the polymeric materials onto the nanoparticle's surface. This technique provides various advantages such as precise control over the thickness, structure, and density of the polymeric layer. Apart from these, the AuNPs synthesized by this method possesses the chemically bonded scaffolds stabilization. These AuNPs are more robust as compared to those, which are synthesized by physiosorption using block copolymer micelles, water-soluble polymers, or star block copolymers. Using this method there are a number of strategies have been reported. For instance, the grafting of poly(methyl methacrylate) was established on to the AuNPs surface following the living radical polymerization (Mandal et al. 2002). Using similar approach, in another report, poly(*N*-butylacrylate) have been grown following atom transfer radical polymerization (Nuß et al. 2001). In addition to these, biopolymers *viz.* oligonucleotide, and peptides have also been reported on the surface of AuNPs followed by the propagation of the grafted molecules. For instance, a single-stranded oligonucleotide grafting was achieved onto the AuNPs with the help of thiol-linked primer-based passivation followed by DNA polymerization (Zhao et al. 2006). In another strategy, the AuNPs are stabilized using peptide chains, which were synthesized by the grafting of sulfhydryl amine groups onto the AuNPs followed by enzymatic peptide elongation. For instance, Higuchi and co-workers reported grafting of alpha-helical poly(gamma-methyl L-glutamate-co-L-glutamic acid) bio-polymeric moieties onto the surface of AuNPs (Higuchi et al. 2007).

Grafting-to technique

In "Grafting to" approach, gold cores are synthesized in polymer aggregates. The major advantage of this method is the availability of various polymers for functionalization. Since this follows a one-pot synthesis method, reacting materials are mixed in a single vessel thereby reducing a number of laborious steps involve in "grafting-from" technique eventually making the synthesis easy. In this method, two types of polymers are commonly used, one with the sulfur-containing group at the terminal end and other terminated with a sulfur-free group. Polymers terminated with a sulfur-containing group such as *di*-thioester, *tri*-thioester, thiol, thioether, and disulfide provide chemical-bonded shell layers around the gold cores (Liu et al. 2007; Aqil et al. 2008). Synthesis of these polymers was done by a radical polymerization using chain transfer reagents containing sulfur atoms (Wang et al. 2007). In polymeric aggregates without sulfur, evolution of gold cores results in gold nanocomposites in which the polymers interact with gold cores through multi-point physical adsorption (Sakai and Alexandridis 2004). However, these gold nanocomposites are unstable and the polymer has a high chance of getting detached from the AuNP

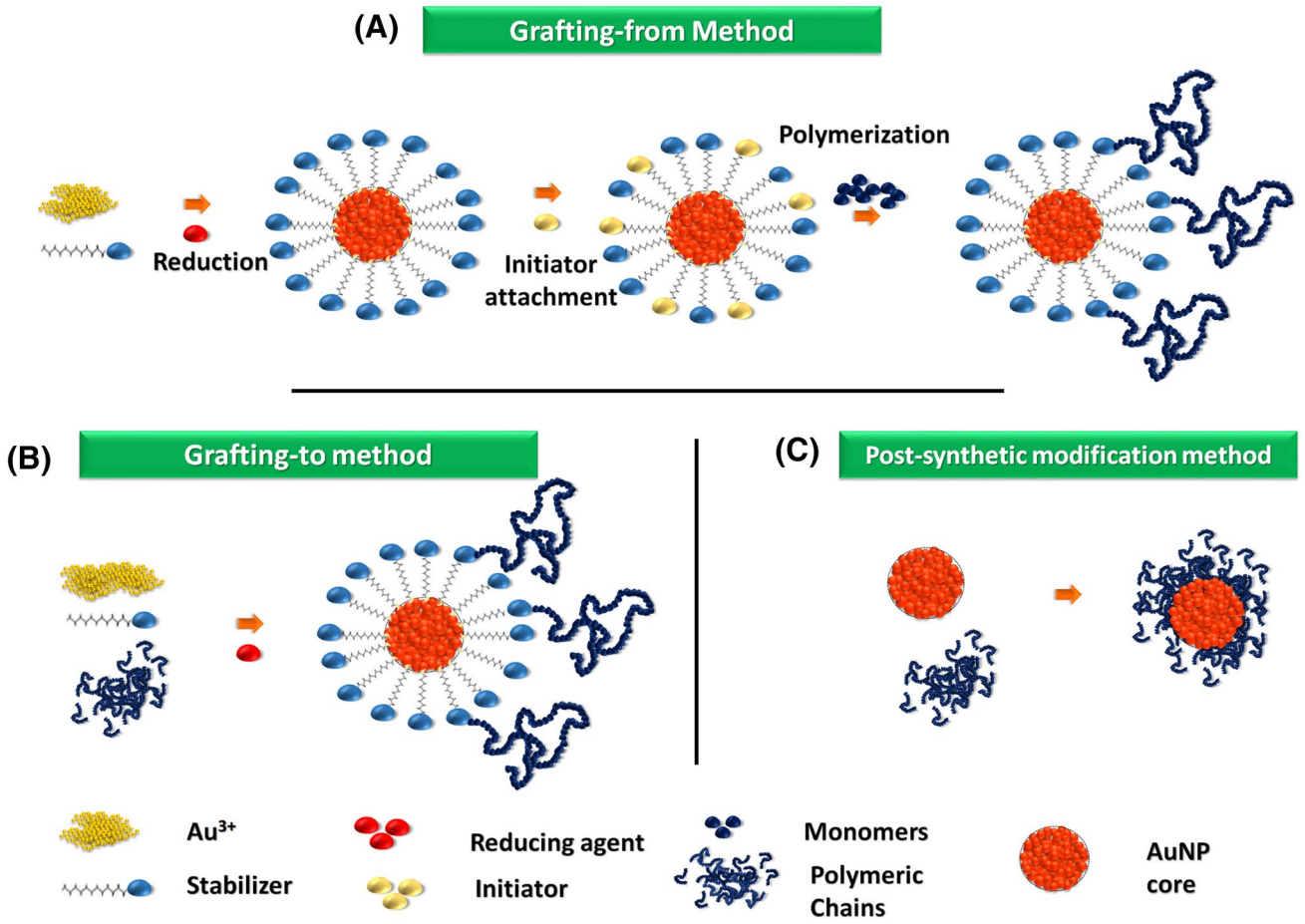

Fig. 4 Schematic representation of the polymer-stabilized AuNPs synthesis using **(a)** grafting-from, **(b)** grafting-to, and **(c)** post-synthetic modification techniques

surface because of the lack of stable chemical bonds. This can be overcome by cross-linking the polymer network or by the use of unimolecular micelles (Filali et al. 2005). This method has been used for the synthesis of AuNPs functionalized with artificial polymers, such as: PVP (Mohamed et al. 2017), poly(vinyl pyridine) (Zhang et al. 2018), PEG (Ocal et al. 2018), PVA (Kwiatkowska et al. 2018), PMMA (Zepon et al. 2015), PEI (Lazarus and Singh 2016), PDDA (Liu et al. 2016) as well as biopolymers (Chowdhury et al. 2018).

Post-synthetic modification techniques

In post-synthetic modification methods, AuNPs are first generated through conventional methods followed by functionalization (Kang and Taton 2005). AuNPs have been covalently conjugated with polymers having thiol groups, while the polymers devoid of thiol moieties were attached through physical adsorption onto the AuNPs surface. Similarly, biopolymers have also been used for the surface functionalization using the similar approach. Due to these distinctive properties and non-toxic nature, oligonucleotide-functionalized AuNPs have been used for highly sensitive and selective assays in detecting biomolecules and thus find several applications in biosensing, disease diagnostics, and gene expression studies. Moreover, due to their greater affinity towards DNA molecules, these are frequently used as non-viral vector for gene delivery (Biju 2014; Sahoo et al. 2017). In such examples, alkyl thiol-terminated oligonucleotide-functionalized AuNPs were synthesized with high stability in saline condition (Briley et al. 2015). Enzymes, peptides, antibodies, aptamer, etc., have also been used for the AuNPs functionalization in place of the chemical reagents (Baranwal et al. 2016; Kumar et al. 2008; Mahato et al. 2018b). So far, several applications have been reported using the AuNPs synthesized from these methods including DNA intercalation study (Wang et al. 2002), polynucleotides detection (Giljohann et al. 2010), and a number of protein detections.

Modification using silica

Silica has extensively been used for passivating the AuNPs, where a thin shell has been coated over NPs to prevent various detrimental interactions between proteins and other molecules with the nanoparticle's surface. This step is followed by the binding of various molecules of interest, viz. spacer, target or coating molecule to the flanking linker on the surface of NPs. Thereafter, the functionalized NPs are sorted according to the number of bound molecules using various chromatographic techniques which also allow the selection of homo-functionalized NPs (Lévy et al. 2006). The silica coating onto the AuNPs greatly enhances its chemical stability against aggregation. These modifications are in general introduced using Stöber method, where tetraethylorthosilicate is used for passivation of gold core (Stöber et al. 1968). For instance, silica-coated AuNPs have been synthesized using (3-aminopropyl)trimethoxysilane configuring alkoxide flanking groups outwards from AuNPs (Liz-Marzán et al. 1996). Silica coating onto the AuNPs greatly enhances the chemical stability against aggregation and its solubility in different solvents. These modifications are also introduced using Stöber method, where the solution of tetra ethylorthosilicate is used in different alcohols such as methanol, ethanol, and isopropanol with ammonia. The resulting solution is then stirred to obtain the silica-coated NPs depending on the type of silicate ester and alcohol used and also on their volume ratios (Stöber et al. 1968). Thin silica shell-based AuNPs passivation has also been reported by Liu and Han, which has shown excellent biocompatibility and has been used in various colorimetric diagnostics, photothermal therapy, and SERS- based detections (Liu and Han 2010). In addition, functionalization of the silica-coated NPs surface with amino-, mercapto- and carboxy-terminated silanes allows the conjugation of other materials for further secondary modifications (Lee et al. 2008).

Applications of functionalized AuNPs

Functionalized AuNPs have extensively been used in various biomedical applications. So far, functionalized AuNPs have found in numerous applications of various fields such as electronics, photodynamic therapy, drug delivery and targeting, sensors, probes, diagnostics, and catalysis (Chandra et al. 2010, 2013b; Kumar et al. 2015). The potential applications of AuNPs in clinical and biomedical domains are described under various categories as follows.

Diagnostic applications

The unique optoelectronic properties, viz. SPR, Raman scattering, and fluorescence quenching led down the AuNPs in various diagnostic applications (Chandra 2016; Mahato et al. 2016a). Upon the exposure of electromagnetic radiation, the conduction electron (or plasmons) starts to oscillate on the surface of AuNPs. The coherent oscillation of the metal free electrons in resonance with the electromagnetic field also called as SPR develops strong electromagnetic fields onto the surface of particles. This subsequently enhances radiative properties such as absorption and scattering, as well as non-radiative properties, which eventually help to monitor the biomolecules. These, surface functionalities show the size-dependent SPR properties. For example, the thiol-stabilized AuNPs (diameter ≈ 5 nm) exhibit SPR at 530 nm, whereas amine-stabilized AuNPs (diameter ≈ 7 nm) exhibit SPR at 540 nm. These SPR properties of AuNPs are useful for biomolecular detection in real time with respect to the changes in refractive index upon binding to thin gold films (Liedberg et al. 1983). The shift in SPR due to the molecular interactions has been exploited for building various diagnostic strategies. For instance, Taton et al. has developed a technique that is capable to monitor these shifts upon nucleic acid interactions (Taton et al. 2000). The plasmonic effects of AuNPs have also led to the development of convenient colorimetric assays. These are based on the fact that the interacting electric fields of aggregating AuNPs have a tendency to lower the resonant frequency of plasmon oscillations, resulting in a visible color change with either bathochromic or hypsochromic shifting of the initial frequency (Srivastava et al. 2005). In such colorimetric assays, the color change is dependent on the action of target analyte, which either directly or indirectly triggers the further states of AuNPs aggregation or re-dispersion. In addition, AuNPs have been modified with linker molecules that can link them together in the presence of a molecule of interest. These AuNP-based colorimetric assays have been used in the detection of specific DNA strands, proteins, and small molecules. For instance, in dipstick-type pregnancy testing kits, AuNPs are modified with secondary antibodies against human gonadotropin hormone that subsequently binds to primary antibodies arranged over a small area to the dipstick (Fig. 5a) (Tanaka et al. 2006). In presence of the target analyte, the binding complex forms in a testing area consisting secondary antibody-conjugated AuNPs, analyte, and primary antibodies, resulting in the change in SPR properties of the AuNPs resulting the appearance of color (Stockman 2011; Tanaka et al. 2006).

Fluorescence resonance energy transfer (FRET) is a distance-dependent energy transfer-based technique, where a donor chromophore supplies emissive energy to the receptor counterpart after getting excited leading to the increased fluorescence intensity of the receptor counterpart of the FRET pair. For an excellent FRET-based optical quenching, AuNPs are a suitable candidate as it possesses high molar extinction coefficient and large energy bandwidth (Jain et al.

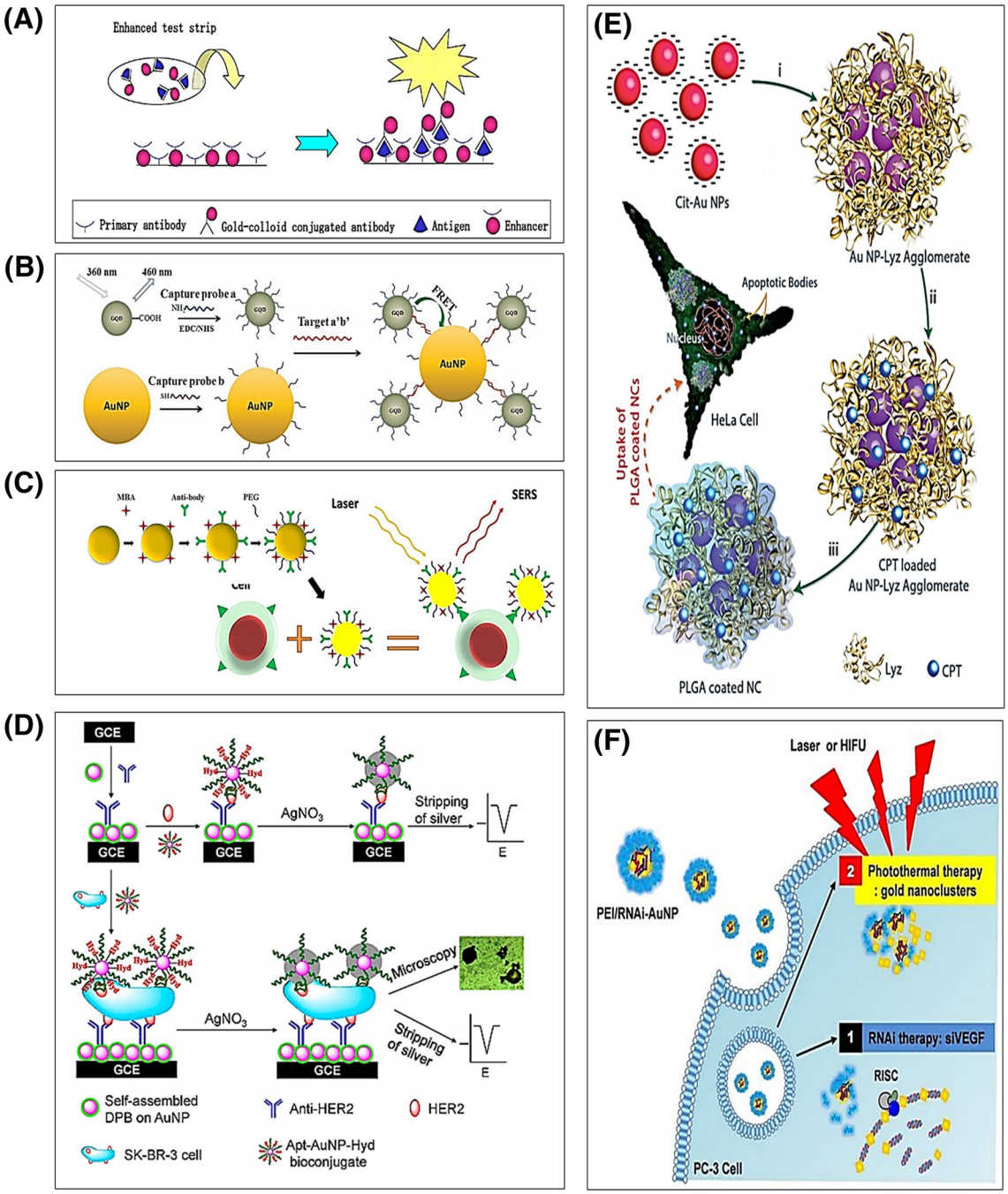

Fig. 5 Illustrations for different applications of functionalized AuNPs, where **(a)** shows the schematic of dipstick-type diagnostic device based on antibody-coated AuNPs for colorimetric detection (Reprinted with permission of Tanaka et al.; copyright Springer). **b** Shows functionalized AuNP–GDQ FRET pair-based detection of mecA gene sequence of Staphylococcus aureus (Reprinted with permission of Shi et al.; copyright Elsevier). **c** Shows functionalized AuNP-based SERS strategy for cell imaging (Reprinted with permission of Zhang et al.; copyright Springer). **d** Shows simultaneous detection and bio-imaging based on aptamer-based functionalized AuNPs (Reprinted with permission of Zhu et al.; copyright the American Chemical Society). **e** Shows co-functionalization of AuNPs and protein using polymers as nano-carrier for delivery of hydrophobic anticancer drug camptothecin (Reprinted with permission of Khandalia et al.; copyright the Royal Society of Chemistry). **f** Shows the anti-VEGF siRNA functionalized AuNP-based combinatorial theranostic strategies targeting early tumor cells (Reprinted with permission of Son et al.; copyright Theranostics)

2007). Using AuNP-assisted FRET technique, Zhang et al. have reported a cholesterol sensor by functionalizing the AuNPs with β-cyclodextrin (Zhang et al. 2008). Additionally, researchers have developed several assays to monitor the cleavage of DNA by nucleases and reported the biomolecular detection up to femtomolar concentrations (Ray et al. 2006). In addition to this, accuracy has been enhanced using multicolored oligonucleotide-functionalized organic dye with AuNPs as nanoprobes (Ray et al. 2007). FRET-based assays have also been utilized to detect specific gene sequences. For instance, Shi *et al*. have developed novel FRET-based biosensor on graphene quantum dots and AuNPs for ultralow detection of a gene from *Staphylococcus aureus*, indicating immense application in medical diagnostics (Shi et al. 2015) (Fig. 5b).

Conventionally, Raman scattering has been used for various detections exploiting the intrinsic spectroscopic properties of analyte molecules but due to their poor intensities limits the usage in various diagnostic applications. Therefore, AuNP-assisted Raman spectroscopy has been adopted to overcome such limitations by employing AuNPs, which is also called surface enhanced Raman spectroscopy (SERS). These systems utilizes the intrinsic properties of the AuNPs for SERS phenomena (Talley et al. 2005; Bellamy and Garthwaite 2001). For instance, a tumor cell detection has been reported by Zhang et al. based on the AuNP-assisted SERS, where the antibody-tagged AuNPs were used (Zhang et al. 2016) and showed excellent analytical performance (Fig. 5c). SERS-based techniques have been found great attention in recent days due to their various advantages, viz. high quality, distinct, and noise-free signals over other diagnostic techniques. Furthermore, the tunability of these SERS-based properties have also been achieved with size, shape, orientation, and the aggregation of AuNPs, which makes the functionalization of AuNPs compatible for barcodes or recognition elements in developing various unique analytic tools (Zheng et al. 2012).

Sensors and biosensors

AuNP's fascinating properties have extensively been utilized to design a number of bio/chemical sensors of optical and electrochemical formats (Kumar et al. 2015; Won et al. 2013; Zhu et al. 2012a; Chandra 2015). The smaller size and high aspect ratio of AuNPs provide stable immobilization of large numbers of biomolecules onto its surface while retaining their biological activities (Chandra et al. 2013b). Therefore, AuNPs are widely used as signal amplification tags in different types of biosensors because of its light-scattering, conducting, and local electromagnetic field enhancement properties (Mahato et al. 2016b; Mandal et al. 2018). Using these properties of AuNPs, various detection strategies have been employed for sensitive and selective detection of target DNA via. sequence-specific hybridization between the target and single-stranded oligonucleotide probe-conjugated AuNPs (Lyon et al. 1998; Spampinato et al. 2016; Bhatnagar et al. 2018; Chandra 2013). A prototype has been developed based on the oligonucleotide probe-conjugated AuNPs as SPR amplification tags that have satisfactorily enhanced the sensitivity by 1000-folds (He et al. 2000). Apart from these, a DNA fluoro-biosensor using a cerium complex $Ce(QS)_2Cl$ and thiolated probe-DNA with functionalized AuNPs have been reported based on DNA hybridization-mediated fluorescence quenching. Similarly, in another work, researchers used AuNPs as both nano-scaffolds for the attachment of capture sequences and as nano-quenchers of fluorophores attached to detect sequences, where 5′-thiolated 12-mer oligonucleotide-functionalized AuNPs were used for sequence-specific detection of target DNAs with a 2-nM detection limit (Wu et al. 2006). In another strategy, an ultra-selective rapid colorimetric biosensor for detecting the breast cancer gene BRAC1 using the DNA–AuNPs hybrid (Oh and Lee 2011). Apart from these, AuNP-based optical probes have also been used for clinical diagnosis of aminothiols, viz. cysteine, homo-cysteine, and glutathione (Xiao et al. 2012). Glycol-conjugated AuNPs have also been employed for selective and sensitive optical detection of a mannose-binding protein complex (Concanavalin A) based on surface plasmon absorption with reported excellent analytical performances, where the dynamic range of 12–45 nM was reported with the detection limit of 4.0 nM (Watanabe et al. 2012). Using AuNPs, there are a number of biosensing prototypes been reported based on the dual signal (optical/electrochemical) transduction. For instance, Boca et al. have demonstrated dual signal-based electrical/optical proof of concept biosensing prototype exploiting the nano-gaps formed during the self-assembly of AuNPs. This showed excellent SERS capabilities and chemi-resistivity of nano-gap AuNPs for the detection of 4-mercaptophenyl boronic acid (Boca et al. 2015). In another report, an aptamer-based AuNP-functionalized biosensor has been developed showing high sensitivity (20 nM) for biomolecular analysis using avidin as a model compound. The developed facile sensor was anticipated to be applied for *in vitro* analysis (Hernandez et al. 2009). Excellent electrical conductivity, high surface area, and catalytic properties of AuNPs are suitable for the electrochemical biosensing where the electrical responses generated are directly proportional to the analyte concentrations (Agrawal et al. 2013; Maurya et al. 2016). Until now, several electrochemical biosensors have been reported for detection of a number of analytes (Chandra 2016; Mahato et al. 2017). An electrochemical bifunctional nanosensor has been developed by Zhu et al. for the detection of HER2 positive breast cancer cells and HER2 protein biomarker

using bioconjugate comprising hydrazine–AuNP–aptamer in a single sensor design (Zhu et al. 2012b) (Fig. 5d). This study elaborates the importance of AuNPs in nanobioconjugate development for biorecognition and also as a signal amplifier in a single experimental setting. In another study, AuNPs functionalized with thiol-modified receptor for glucose biosensing has been developed to monitor the glucose level of diabetic patients (Spampinato et al. 2016). In addition, functionalized AuNPs assisted strategies are constantly adding the qualities to various biosensors in terms of sensitivity, selectivity, limit of detection, dynamic range and compatible with numerous analytes including drugs, neurotransmitters, heavy metal ions, bacterial/cancer cells, and other metabolically active molecules (Zhu et al. 2012c; Chandra et al. 2011b; Kashish et al. 2017; Chung et al. 2018; Akhtar et al. 2018; Baranwal and Chandra 2018).

Bio-imaging

AuNPs and its composites have widely been used for bio-imaging applications exploiting their strong radiative properties. The AuNPs facilitate the biological features to visualize the surfaces under dark field microscopy. For instance, anti-epidermal growth factor receptor (anti-EGFR) antibody-functionalized AuNPs (40 nm) were used for the bio-imaging of overexpressed biomarker protein on cancer cells exploiting the SPR response of tagged AuNPs (El-Sayed et al. 2005). The SPR responses of these functionalized NPs irradiation appear in green light range (530 nm), which helps to visualize the immune interactions of tagged antibody to the present biomarker resulting the highly specific bio-imaging. Apart from this, the optimized geometries of AuNPs such as rods or cubes make them optimal tools for two-photon luminescence technique which uses a femtosecond near-infrared region laser excitation (Dreaden et al. 2012). This technique is known for its nonlinear optical imaging in near-infrared region where water and biomolecules show minimum absorption, thereby reducing background noises and increasing spatial resolution. These optical signatures have helped researchers to develop *in vitro* and *in vivo* imaging methods for detection of cancer and other living cells. For instance, Durr et al. used gold nanorods functionalized with anti-EGFR antibodies based on the above techniques for the molecular imaging of cancer cells at different depths within the tissues (Durr et al. 2007). Apart from these approaches, Chandra et al. have reported AuNPs mediated label free bio-imaging platform for cancer cells detection through the interaction between daunomycin and cell surface receptors. The bioimaging system, in this case, was also confirmed using electrochemical impedance spectroscopy (Chandra et al. 2011a).

Therapeutics

Functionalized AuNPs also show therapeutic effects including photothermal therapy (PTT) where the thermoablative properties of AuNPs are exploited to generate heat. The excitation of the AuNPs by near infrared or radio frequency radiations leads to the burning of the targeted cells (Huang et al. 2009; Jain et al. 2008). For example, a poly ethylene glycol-coated gold nanorods were used for tumor inhibition in an animal model using near-infrared PTT (Dreaden et al. 2012). Functionalization of AuNPs using DNA aptamers has been studied for various therapeutic studies including PTT and photodynamic therapies. In addition to this, these aptamer-functionalized AuNPs have also been studied for anticancer and antiviral therapies (Wang et al. 2016). Similarly, in a most recent study, AuNPs conjugated with DNA aptamers have found to be enhanced the therapeutic efficiency by inducing specificity, stability, uptake efficiencies of biomolecules. For instance, an aptamer–AuNP–graphene oxide nanocomposite developed by Wang et al. exhibited PTT effects even in an ultralow concentration of overexpressed MUC1 cancer cells (MCF-7) without affecting the healthy cells (Wang et al. 2016).

Drug delivery

Furthermore, AuNPs found use in the targeted delivery of various payloads ranging from small drug molecules to biomacromolecules, owing to their low cytotoxicity, good cell permeability, and high drug-loading efficacies, stemming from their intrinsic greater surface-to-volume ratio. The attachment of payload can be achieved either by covalent chemical conjugation of small molecules, viz. drugs and neurotransmitters, or by non-covalent attachments, such as; electrostatic interactions as in the case of bio-macromolecules, e.g., peptides (Khandelia et al. 2014). The modes of attachment sometimes play an important role in delivering of species. In the case of covalent attachment of pro-drugs, they are delivered which are then processed in intracellular environment before assimilation, while the active drugs are generally attached with non-covalent means showing better release (Morgan et al. 2006). The release of the payloads can be triggered by various internal [e.g., glutathione (Hong et al. 2006), or pH (Polizzi et al. 2007)] or external stimuli (e.g., light) (Han et al. 2006). In general, AuNPs assisted delivery of molecules are optimized by tuning the particle size or by altering surface functionalization steps. For example, secondary coating with antibiofouling agents (viz. thiol-derivatized poly-ethylene glycol) was reported for delaying the response from reticuloendothelial system

that acts as a biological barrier for drug delivery, which was reported the delayed delivery by 0.5–72 h in a mice model, claiming delivery clearance of approximately 150-fold than unmodified cetyltrimethylammonium bromide-capped AuNPs (Niidome et al. 2006). Different targeting moieties such as proteins, peptides, antibodies, and small molecules including folic acid and paclitaxel have also been attached to the AuNPs surface to facilitate selective cellular uptake and internalization of the drug-loaded nanocarriers. At the same time to achieve a highly specific targeted drug delivery to heterogeneous population of cancer cells in solid tumors, several receptor molecules (antibody, aptamer, peptide, etc.) are also attached onto the surface of AuNPs. In addition to this, several platforms have been demonstrated showing exciting results in delivering molecules into tumors (El-Sayed et al. 2005; Visaria et al. 2006; Huang et al. 2006a; Paciotti et al. 2006). For instance, Khandalia et al. have reported polymer-coated NP–protein conjugate to deliver the drug in the human cell lines and successfully induced the apoptosis to the target cells (Fig. 5e) (Khandelia et al. 2014). Some of the commonly FDA approved NPs-based drugs including paclitaxel, and doxorubicin were successfully cleared the clinical trial and used in a metastatic breast cancer phase III multiple-myeloma treatment in metastatic ovarian cancer, respectively (Singh et al. 2015).

Theranostics

Theranostics is an approach which provides the simultaneous benefits of therapeutics as well as imaging and diagnostics on a single platform (Chandra 2016). Since AuNPs exhibit several unique features such as SPR and absorption of near-infrared region of electrochemical radiation, by virtue of these the AuNPs show photothermal properties. Such properties have been exploited for targeted detections of cancerous/tumorigenic cells and their destruction simultaneously. The pioneering works on theranostics applications using the gold nanoshells were reported by Loo et al. (2005) and gold nano-spheres by Lapotko (2009). Following the trends, so far, a number of theranostic strategies have been reported using AuNPs for various types of cancers. For instance, AuNPs have been used for diagnosis and treatment of gastrointestinal (GI) cancers by targeting GI adenocarcinoma cells via. thermal induction (Singh et al. 2015). Here, the heating effects of AuNPs uncouple the heat sensitive chemical bonds facilitating a release of drugs directly at the target site (Singh et al. 2015). The detailed articles of this domain have been comprehensively reported elsewhere which includes theranostic applications of AuNPs for imaging, photothermal therapy (Curry et al. 2014), nanocardiology (Spivak et al. 2013), single nanomaterial based treatment (Vinhas et al. 2015), and in theranostics oncology (Akhter et al. 2012) along with multifunctional composites (Khlebtsov et al. 2013). So far various strategies have been adopted including AuNP-based that have been developed by co-encapsulation of AuNPs with chemotherapeutic drugs including paclitaxel (Muthu et al. 2014), doxorubicin (Chen et al. 2013), and daunomycin (Chandra et al. 2013a) for efficient theranostic applications. In one of such examples, Shao et al. have developed an ellipsoidal NP–drug conjugate, which can harness the synergy of photothermally activated physical and biological effects for therapeutic goals. (Shao et al. 2013). In another example, the tumor necrosis factor-alpha coated gold nanospheres (Au-TNF-α) have been used for the treatment followed by heating with laser pulses. In addition, higher efficacy has been obtained in pulsating laser-mediated treatment in *in vivo* studies carried out using mice models. In addition to these advancements, functionalized AuNPs have also reported to induce combinatorial theranostic effects to the targeted cells. In an article reported by Son et al. demonstrated that AuNPs functionalized with anti-VEGF siRNA for the cancer eradication in later stages (Fig. 5f) (Son et al. 2017).

Conclusions and future prospects

As per the above discussion on the synthesis, surface modification, and application potentials of AuNPs, it is evident that it is excellently compatible to the nanoplatforms for various biomedical applications. In particular, AuNPs are passivated with a variety of ligands, functional groups, imaging labels, therapeutic drugs, and carrier molecules before the actual applications. Commonly, the functionalization of the AuNPs is achieved by modifying its surface either with linker moieties followed by modification of capping agent of interest or by place-exchange reaction with originally stabilized ligand or by linking to the shell of stabilizing molecules. Thus, the functionalized AuNPs found an important place for serving a number of biomedical applications, viz. sensitive detection of biomolecules, cellular imaging, and drug delivery agent. In the recent era, tremendous researches on AuNP-based nano-platforms have been fabricated for the same purpose, yet there is an enormous scope of improvements to enhance their applicability in various biomedical applications. Few common instances to be considered as future prospects are as follows:

- The AuNP-assisted optical imaging is possible, however, there are no models which can quantify the optical signals accurately particularly in deeper tissues to provide sufficient information about the target disease.
- There are several reports that have used AuNP-based models for tumor/cancer therapy, but none of them has addressed the generalized case, which can target mul-

tiple closely related cells specifically without affecting surrounded healthy cells.

- Several AuNPs-based sensing devices and many proof-of-concept prototypes have been reported for various clinical pathogens/samples, yet very few prototypes have been commercialized to provide personalized diagnostic platform. Therefore, more efforts should be given to improvise the existing strategies for better high throughput translational prototypes.
- A number of AuNPs-based drug delivery systems have been reported, yet the therapeutic efficacy of these are limited with respect to dosage and target-specific non-toxic delivery.
- AuNPs-based photothermal therapy has widely been reported for the treatment of cancerous cells, but suffers from the non-specific damage healthy cells due to the uncontrolled and uneven heating.
- AuNPs-based theranostic strategies are fascinating in biomedical science; however, there are much remains to be done to achieve the real goals.

Therefore, the field remains open to many important discoveries to find new methods of synthesizing AuNPs with compounds that would promote excellent biocompatibility and would make them useful for diagnostics, bioimaging, and therapeutics. Hence, the future work should be directed towards better understanding of the behavior of AuNPs in biological/real systems to overcome the limitations of conventionally developed AuNPs, which can assist the next-generation need of engineering and medicine by improving the clinical diagnostic platform.

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Compliance with ethical standards

Conflict of interest Authors report no conflict of interest in this work.

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