Colloid and Interface Science Communications 35 (2020) 100244

Contents lists available at ScienceDirect

Colloid and Interface Science Communications

journal homepage: www.elsevier.com/locate/colcom

Emerging trends in clinical implications of bio-conjugated silver nanoparticles in drug delivery

Parteek Prasher[a,c], Mousmee Sharma[b,c,*], Harish Mudila[d], Gaurav Gupta[e], Abhishek Kumar Sharma[f], Deepak Kumar[f], Hamid A. Bakshi[h], Poonam Negi[f], Deepak N. Kapoor[f], Dinesh Kumar Chellappan[g], Murtaza M. Tambuwala[h], Kamal Dua[f,i,j]

[a] Department of Chemistry, University of Petroleum & Energy Studies, Dehradun 248007, India
[b] Department of Chemistry, Uttaranchal University, Dehradun 248007, India
[c] UGC Sponsored Centre for Advanced Studies, Department of Chemistry, Guru Nanak Dev University, Amritsar 143005, India
[d] Department of Chemistry, Lovely Professional University, Phagwara 144411, India
[e] School of Pharmacy, Suresh Gyan Vihar University, Jagatpura 302 017, Jaipur, India
[f] School of Pharmaceutical Sciences, Shoolini University, Bajhol, Sultanpur, Solan, Himachal Pradesh 173 229, India
[g] Department of Life Sciences, School of Pharmacy, International Medical University, Bukit Jalil, Kuala Lumpur 57000, Malaysia
[h] School of Pharmacy and Pharmaceutical Science, Ulster University, Coleraine, County Londonderry, Northern Ireland BT52 1SA, UK
[i] Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Sydney, NSW 2007, Australia
[j] Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute (HMRI) & School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, NSW 2308, Australia

ARTICLE INFO

Keywords:
AgNPs
Bio-conjugation
Bio-functionalize
Nanopharmaceuticals
Biosensors

ABSTRACT

From nanopharmaceutics to renewable energy, silver nanoparticles (AgNPs) present innumerable applications in the contemporary era. However, the associated toxicity to the biosystems limits their application. Effective utilization of AgNPs, therefore, requires their surface conjugation with biologically benevolent moieties that enhance the bio-acceptability of silver-based nanosystems, and supplementary functionalities for further extension of their unique applications. The clinical importance of AgNPs was established long ago, but their clinical utilization has been explored only recently with the phenomenon of bio-conjugation. The biomolecule-conjugated AgNPs present operable solutions for tedious clinical complications of the present era, such as multidrug resistance, designing of pharmaceuticals with improved bioavailability, superior drug delivery vehicles and in situ bio imaging of important metabolites that utilize the biomolecule-anchored surface engineered AgNPs. This review epigrammatically discusses some interesting clinical applications of surface conjugated AgNPs with biomolecules such as peptides, nucleic acids, amino acids and antibodies in the current nanopharmaceutical paradigm.

1. Introduction

Silver nanoparticles (AgNPs) offer an array of industrial applications in multidisciplinary domains and hence qualify as the most exploitable contemporary material [1] owing to a tunable physicochemical profile, characteristic surface plasmon resonance and surface functionalization [2]. The tailored AgNPs also offer workable solutions for countering the emerging complexities related to multidrug resistance [3], probing

List of Abbreviations: Abbreviations, Elongated forms; AgNPs, Silver nanoparticles; ROS, Reactive oxygen species; PVP, Poly-(vinyl-pyrrolidone); MUDA, 11-Mercaptoundecanoic acid; MPS, 3-(Trimethoxysilyl) propyl methacrylate; CTAB, Cetyl trimethylammonium bromide; CTAN, Cetyltrimethylammonium nitrate; APTMS, 3-Aminopropyltrimethoxysilane; TEOS, Tetraethyl orthosilicate; PEG, Polyethylene glycol; EDC, 1-Ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride; PDP-PE, 1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine-N-[3-(2-pyridyldithio)propionate]; PDPSA, 3-Pentadecyl phenol–4-sulphonic acid; PDP-PEG-DSPE, 1,2-Distearoyl-sn-glycero-3-phosphoethanolamine-N-[PDP(polyethylene glycol)]; Sulfo-SMCC, Sulfosuccinimidyl-4-(maleimidomethyl) cyclohexane-1-carboxylate; SATA, N-succinimidyl-S-acetylthioacetate; SPDP, N-succinimidyl-3-(2-pyridyldithio) propionate; TBA, Thiobarbituric acid; NHS, N-hydroxysuccinimide; Sulfo-NHS, Nhydroxysulfoxuccinimide; RGD, Arginylglycylaspartic acid; AMPs, Antimicrobial peptides; MDR, Multidrug resistance; TCEP, Tris(2-carboxyethyl) phosphine; MIC, Minimum inhibitory concentration; SWCNT, Single walled carbon-nanotubes; MPA, 2-Mercaptopropanoic acid; CPP, Cationic cell-penetrating peptides; MPA, Mercaptopropanoic acid; MB, Magnetic beads; TPE, Two-photon excitation; FRET, Fluorescence resonance energy transfer; AGB1, Aflatoxin B1; Cdna, Complementary DNA; IgG, Immunoglobulin G

* Corresponding author at: Department of Chemistry, Uttaranchal University, Dehradun 248007, India.
E-mail address: mousmee.sharma90@gmail.com (M. Sharma).

https://doi.org/10.1016/j.colcom.2020.100244
Received 6 December 2019; Received in revised form 29 January 2020; Accepted 30 January 2020
Available online 07 February 2020

biomolecule profile [4], effective soil and water management [5] and in harnessing renewable energy [6]. Apparently, the diverse morphologies of capped AgNPs, their maneuverable interactions with biomolecules of interest coupled with a considerable bioavailability, bioactivity [7], and a sizeable oligodynamic effect [8] together with a substantial synergism with the existing pharmaceutics [9–12] justifies a multitude of their current biological applications. However, the development of AgNP-formulations as an integral ingredient at the nano-bio interface necessitates the acknowledgement of their associated cytotoxicity [13], and a mechanistic quantization of interactions between the nanoparticle and its conjugated biomolecule [14]. Notably, on contacting the biological fluids, the nanoparticles reportedly adsorb a proteinaceous corona on their surface [15] that provides them an *in vivo* stability [16], determines the nanoparticle biocompatibility [17] and regulates the interactions of nanoparticle-corona complex with cellular biomolecules [18]. Additionally, an effective nanoparticle concentration and their surface functionalization also determines the concomitant physiological toxicity [19]. An effective, yet benign *in vivo* application of nanoparticles, therefore, requires their conjugation with biologically acceptable molecules or biomolecules [20] or their surface functionalization with physiologically benevolent moieties [21]. AgNP-templated surface functionalization with molecules of interest further extends the prospects of their wide array of clinical applications [22].

2. Surface functionalization of AgNPs

AgNPs represent the most extensively explored contemporary material, despite; the imminent adverse effects of nano-silver formulations that constrain their application in nano-medicine [23]. Reportedly, the chemically synthesized AgNPs induce conformational deformities in the intracellular proteins due to a fragile surface, which undergoes oxidation readily under physiological conditions thereby manifesting several deleterious effects such as oxidative stress [24]. Upon their internalization in the cells, the AgNPs may lose their surface coatings, weakly held functionalities, and develop a protein corona [25] on the peripheral surface that completely conceals their engineered surface, induces an intracellular aggregation thereby marring their unique characteristics [26]. Simultaneously, the corona proteins surrounding the exposed AgNPs surface readily undergo denaturation and structural deformations, [27] thereby, exposing cryptic peptide epitopes that potentially activate the autoimmune responses [28]. In addition, the Ag^+ ions released by the surface oxidation of naked AgNPs *in vivo* by physiological oxidants augment the intracellular production of ROS (reactive oxygen species) causing an irreversible loss to the vital organelles and biomolecules [29] by creating oxidative stress.

In addition, the naked AgNPs reportedly disable the vital cell-signaling pathways, potentially block the cell cycle in S-phase and prompt G1 arrest, thereby inhibiting cell proliferation and promoting apoptosis [30]. However, an appropriate surface functionalization or capping agent provides thermodynamic stability to the AgNPs against the surface corona, thereby improving their intracellular stability while retaining their original tailored characteristics [31]. Various mechanisms validate the role of capping agents on AgNPs, including steric stabilization, stabilization by hydration forces, electrostatic stabilization, depletion stabilization and stabilization using van der Waals forces [32,33]. The resulting surface-functionalized and capped AgNPs function as diagnostic probes, bioimaging agents, drug delivery vehicles and assist in the controlled release of commercial drugs that otherwise possess a low bioavailability profile [34,35]. Similarly, the decoration of AgNPs surface with suitable organic ligands, besides preventing their agglomeration, also offers added functionalities in the form of functional head groups, which acts as useful tools for increasing the compatibility while interacting with another phase [36] thereby, expediting the dispersion of nanoparticle in the target systems [37]. Therefore, the nature of the capping agent assists in tailoring numerous physical and biological properties of AgNPs for addressing a wider range of their applications.

2.1. Aqueous phase stabilization of surface stabilized AgNPs

The synthesis of clinically significant AgNPs with a suitable capping agent occurs principally at high temperatures [38] in the organic phase that allows purging out of the impurities, [39] thereby yielding a crystalline structure and assuring a solution-phase steric stabilization of nanoparticles by the long-chain organic ligands [40,41]. However, these chemically synthesized nanoparticles stabilized with non-polar/hydrophobic organic chains solubilize only in organic solvents, which restrains their direct applications in biological systems, predominantly taking place in an aqueous background [42]. Secondly, the organic phase stabilized surface functionalized AgNPs customarily destabilize in aqueous phase, the unwelcomed event for their direct clinical applications as it manifests considerable toxicity *in vivo* due to the direct exposure of the physiological components to the metallic silver and Ag^+ ions [43]. The engineered AgNPs must be, therefore, surface-functionalized with hydrophilic ligands prior to display superior aqueous compatibility that not only mitigates the physiological toxicity but also augments their bioavailability [44,45]. Fig. 1 displays the contemporary strategies for tailoring the surface of capped AgNPs with biologically gentle, hydrophilic functionalities. In a typical *ligand addition* methodology, the hydrophobic ligand of the capped AgNP anchors to a biocompatible inorganic hydrophilic head group such as silica [46], secondary silanes [47], zinc sulfide [48] to yield the core-shell structures that stabilize the nanoparticle core, in addition to offering ancillary functionalities or chemical functional groups for further functionalization [49,50]. In addition, silica coating also ensures enhanced hydrophilicity, superior colloidal stability and fewer non-specific interactions [51]. A classical synthesis protocol for cultivating a silica shell around AgNP core comprises a preliminary exchange of hydrophobic ligands with primer molecules such as poly-(vinyl-pyrrolidone (PVP) [52], 11-mercaptoundecanoic acid (MUDA) [53], 3-(trimethoxysilyl) propyl methacrylate (MPS) [54], cationic surfactants such as cetyltrimethylammoniumbromide (CTAB) [55], cetyltrimethylammonium nitrate (CTAN) [56] and 3-aminopropyltrimethoxysilane (APTMS) [57]. Afterward, the growth of amorphous silica shell via hydrolysis of sodium silicate [58], tetraethoxysilane [59], tetraethyl orthosilicate (TEOS) [60] proceeds in an alkaline environment to yield Ag-core shell nanostructures. The *ligand exchange* approach comprises the replacement of the previously appended hydrophobic chains present on the surface of AgNPs with strongly bonding hydrophilic ligands that bring the nanoparticles in aqueous phase from the organic phase [61].

The hydrophilic, phase transferring ligands include high affinity, small functional head groups such as amine [62], phosphine [63], carboxyl [64] and thiol groups [65] that support an *in vivo* transmembrane penetration of AgNPs [66]. Nevertheless, these small ligands also stabilize the AgNPs primarily by electrostatic interactions that may lead to coagulation and aggregation of AgNPs on changing the pH and salt concentration of the parent solution [67]. The polymeric ligands such as polyethylene glycol (PEG) serve as hydrophobic ligand exchangers and resolve the humble colloidal stability of small molecules-capped AgNPs [68]. The ether functionality in the PEG backbone employs hydrogen bonding, unlike the electrostatic interactions in case of small ligands; that leads to steric stabilization in an aqueous solution over a wide pH range and even at high salt concentration [69]. In addition, the AgNPs functionalized with PEG display minor nonspecific interactions to biological systems, low cytotoxicity, and superior physiological compatibility [70]. *Encapsulation*, serving as an advanced strategy for phase transfer of functionalized AgNPs to aqueous medium proceeds by surface over-coating of hydrophobic ligand anchored AgNPs with amphiphilic polymers or block co-polymers [71] where the hydrophobic terminal of polymer intercalates with the hydrophobic ligand already present on AgNPs surface and the hydrophilic portion points towards the parent solution [72]. The polar head groups present on amphiphilic polymer provide aqueous stability to the AgNPs and

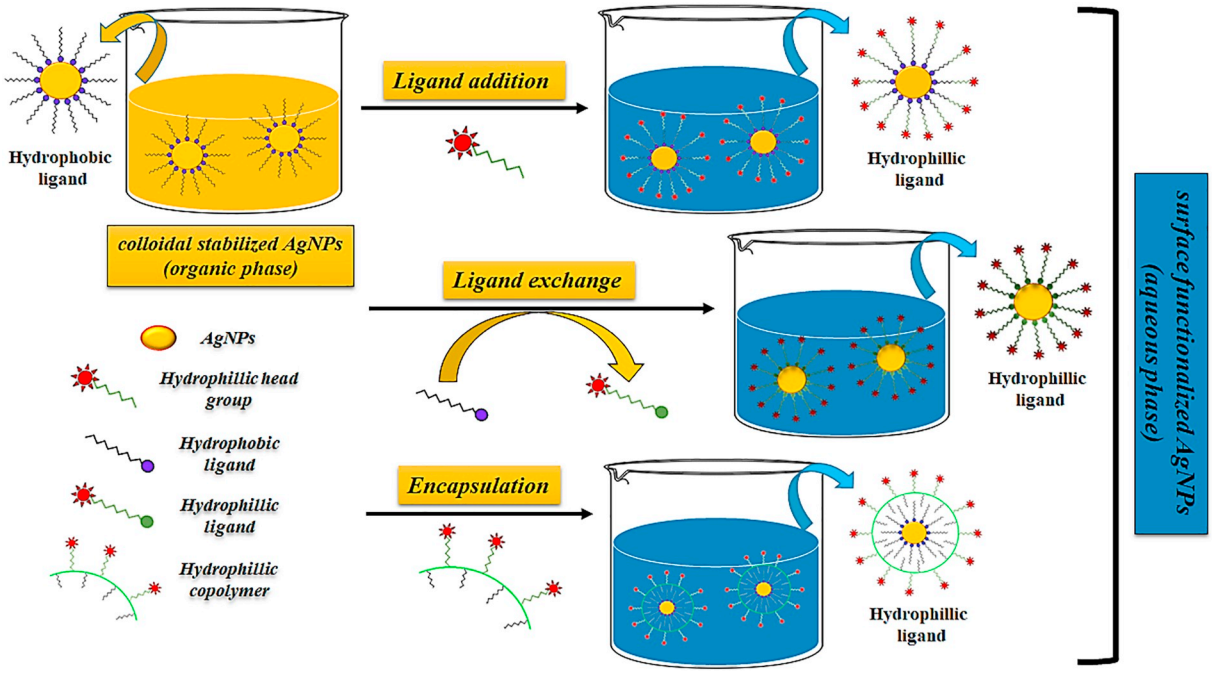

Fig. 1. Phase transfer strategies for obtaining hydrophilic, surface-functionalized AgNPs for their further bioconjugation

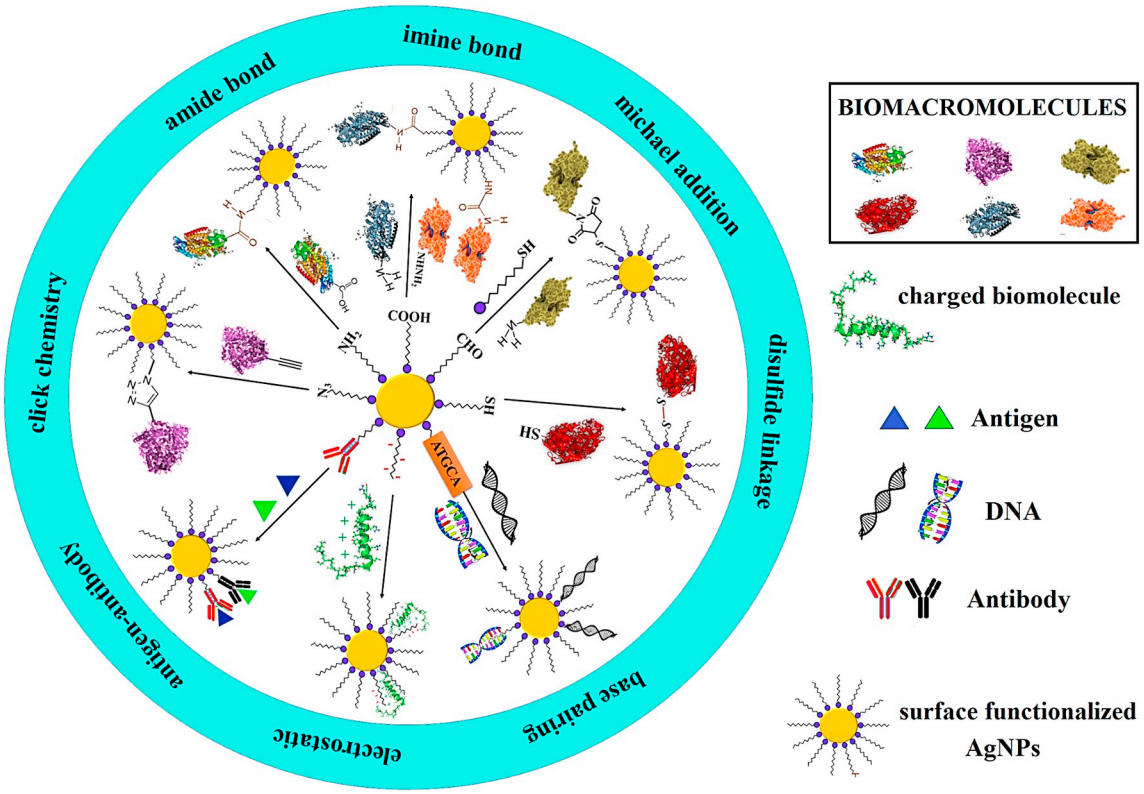

Fig. 2. Strategies for conjugating the aqueous phase stabilized, hydrophilic ligand functionalized AgNPs obtained in Fig. 1 with the desired biomolecules

permits their further bio-conjugation [73]. These strategies afford an effective transfer of colloidal stabilized AgNPs present in organic phase to the aqueous phase, with active head groups present as surface functionalities that improve the physiological acceptance and alleviate the toxicity of nanoparticles [74], in addition to promoting the bio-conjugation of AgNPs with target biomolecules by applying the appropriate synthetic procedures schematically discussed in Fig. 2.

2.2. Surface functionalization of AgNPs for binding to biomolecules

A rationalization for the clinical applications of surface-functionalized AgNPs requires a critical understanding of the nature of interactions between functionalized AgNPs and the target biomolecule [75]. The surface functionalization of AgNPs with a biomolecule of interest alters the surface composition and morphology of nanoparticle [76], offers a compatible interface with the real biological systems, however

sparing its bulk mechanical and physicochemical properties [77]. Surface functionalization leading to enhanced aqueous stability of AgNPs further promotes their conjugation with biomolecules of interest such as amino acids, peptides, nucleic acids, amino acids and antibodies for advanced clinical applications [78]. AgNPs possess an integral ability to interact directly with the biological systems [79] even without the presence of surface functionalities through weak, non-specific non-covalent interactions, but these interactions are non-exploitable and mostly generate undesired effects [80]. The nature of interactions between AgNPs and biomolecules depends on the type of functionality present on the nanoparticle surface and the intensity of its surface charge. Principally, the surface decoration of AgNPs with the amine, carboxylic, thiol, sulfide functionalities serves as a critical step towards their bio-conjugation. The contemporary strategies for bioconjugation of AgNPs include both chemical and physical interactions between the nanosystem and the target biomolecule. The bioconjugation of the surface-functionalized AgNPs tagged with functional head groups to the target biomolecules broadly includes chemistries such as Michael addition between -NH_2 & -CHO through the formation of maleimide, formation of covalent imine, thiol and disulfide linkages, and amide bond formation between the amine-functionalized nanosystems with a carboxylic head group on target biomolecule. 1-Ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride (EDC), sulfo-NHS coupling chemistry also forms an integral part in the contemporary bio-conjugation paradigm. Moreover, the base pairing between the target nucleotide and the complementary AgNP-tagged nucleoside present the most recent advancements in the current nano-bio-conjugation realm (Fig. 2) with extensive applications in molecular medicine and theranostics.

2.2.1. Thiol/sulfide anchoring of AgNPs for conjugation with biomolecules

The interactions of biomolecules containing a thiol functionality with AgNPs have been extensively studied [81] and clinically applied in the emerging enzyme inactivation and enzyme immobilization paradigm, designing free radical scavengers and free radical-directed anticancer nanopharmaceutics, developing novel biometabolite probing biosensors and for evolving antibody-nanoparticle bio-conjugates for effective gene delivery [82]. A nano-bio conjugated disulfide bond typically forms by the reduction of thiol groups present on the functionalized nanoparticle, followed by their subsequent covalent linkage with the corresponding thiolated biomolecule [83]. However, a preliminary surface modification of the nanoparticle with thiol group source serving molecules such as 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine-N-[3-(2-pyridyldithio)propionate] (PDP-PE) [84], 3-pentadecyl phenol–4-sulphonic acid (PDPSA) [85], and 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[PDP(polyethylene glycol)] (PDP-PEG-DSPE) [86] is required for expediting the nano-bio conjugate disulfide covalent bond formation. Other AgNP stabilizing and capping moieties that afford a thiol functionality to the AgNPs for their further bio-conjugation include alkylthiols: $HS(CH_2)_nCH_3$ (n = 11); thioalkyl acids: $HS(CH_2)_nCH_3$ (n = 10); thioalkyl amines: $HS(CH_2)_nNH_2$ (n = 2); and thioalkyl-PEG-R (R = H, CH_3, CH_2COOH, NH_2) [87]. Besides, the strong covalent/ dative linkages and surface adsorption, thiol group also interacts directly with the AgNPs surface through considerable electrostatic interactions between the sulfur atom and the nanoparticle [88]. Furthermore, the thiol-containing biomolecules such as cysteine, cysteamine, homocysteine, glutathione that interact with the nanoparticle surface by non-covalent electrostatic interactions through their 'S' atom under acidic conditions assist in the colloidal stabilization of AgNPs and essentially, serve as linker molecules for tethering AgNPs to the biomolecule of interest [89,90]. The thiol group also offers a flexible reactivity to the cysteine residues that form a significant part of the enzyme active sites (second only after the histidine residues) [91,92]. Moreover, the high-affinity bio-conjugation of cysteine residues with AgNPs with a high binding energy of 65 kcal ol^{-1} further promotes the interaction of thiolated nanoparticles to biomacromolecules such as peptides and enzymes [93,94]. Similarly, the biomolecules tagged with a thiol functionality conjugates to the amine-functionalized AgNPs [95] in the presence of a suitable coupling reagent such as sulfosuccinimidyl-4-(maleimidomethyl) cyclohexane-1-carboxylate (sulfo-SMCC) [96]. The AgNPs fabricated with an aldehyde functionality undergo Michael addition with the amine group present on the target biomolecule, thereby forming maleimide templated AgNP-biomolecule conjugate. Subsequently, the thiol tagged AgNPs act as nucleophiles centered at 'S' atom and anchor directly to the maleimide ring bearing target nano-biomolecular system at its electron-deficient C3/ C4 positions through a thioether bond. The coupling reaction between the thiol group and maleimide occurs rapidly at room temperature and in aqueous solution [97] but with a low selectivity owing to the side reactions, such as intermolecular rearrangement leading to the formation of disulfides [98]. The efficiency of this reaction enhances with activating agents such as N-succinimidyl-S-acetylthioacetate (SATA) [99] or N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP) [100,101]. The maleimide linked AgNPs based bio-conjugates play a significant role as vehicles for effective drug delivery at the antibodies surface [102].

2.2.2. Carboxylic/amine anchoring of AgNPs for conjugation with biomolecules

The citrate ions assist in stabilizing and surface tailoring of engineered AgNPs and in understanding the dynamics of carboxylic functionalized AgNPs [103]. Predominantly, the AgNPs undergo electrostatic stabilization in the presence of a carboxylic group, citrates and polyoxoanions that interact directly with the nanoparticle surface, thereby imparting a negative charge to it [104–107]. Conversely, the deployment of branched polyethyleneimine (PEI) affords an amine functionality on the surface of AgNPs and equips it with a positive charge [108,109].

However, the AgNPs tagged with bifunctional ligands such as thioctic acid, 11-mercaptoundecanoic acid (MUA), thiomalic acid, mercaptoacetic acid, mercaptopropionic acid, mercaptohexanoic acid, and mercaptopropionic sulfonic acid; interact with AgNPs surface through the 'S' atoms present in the chain or in cyclic disulfide ring provides free carboxylate functionalities on the nanoparticle surface. These tags enhance the nanoparticle hydrophilicity, a prerequisite for its conjugation with the target biomolecule [110–113]. Thiobarbituric acid (TBA) also offers bio-conjugable carboxylic functionalization on AgNPs surface by chelating to the nanoparticle surface through 'S' and 'N' atoms, thereby letting free the carboxylic groups. TBA tag also ensures a better nanoparticle stabilization and a superior aqueous dispersibility. Advantageously, the TBA directed carboxylic functionalization also offers clinically exploitable interactions with several proteins residues [114]. Other carboxyl group offering moieties include long-chain unsaturated carboxylates such as oleic acid, elaidic acid, palmitoleic acid, linoleic acid, linolenic acid, and cis-11-eicosenoic acid; where the AgNPs interact with the olefenic positions preferably in a 'cis' configuration and the carboxylic head groups project freely in the colloidal suspension [115]. Besides, the amino acids also form coordinate complexes with the Ag^+ ions through the functionalities such as > C = O, NH_2 and –COOH yielding bio-conjugated AgNPs through an amide bond [116]. The formation of a bio-conjugated amide bond generally occurs in two steps. The first stage involves EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) mediated activation of the carboxylic tag on the participating biomolecules to yield the intermediate O-acylisourea ester, which later reacts with the primary amine tag on the functionalized AgNP to form an amide bond [117]. EDC coupling also extends to the covalent coupling of phosphate groups on nucleic acids to amine-functionalized AgNPs through an NHS-ester intermediate [118] (Fig. 3). Advantageously, the appreciable aqueous solubility of EDC supports its direct application in bio-conjugated bond formation in biological systems, instead of using organic dissolution solvents or amide bond-forming chemical reagents [119]. Secondly, the

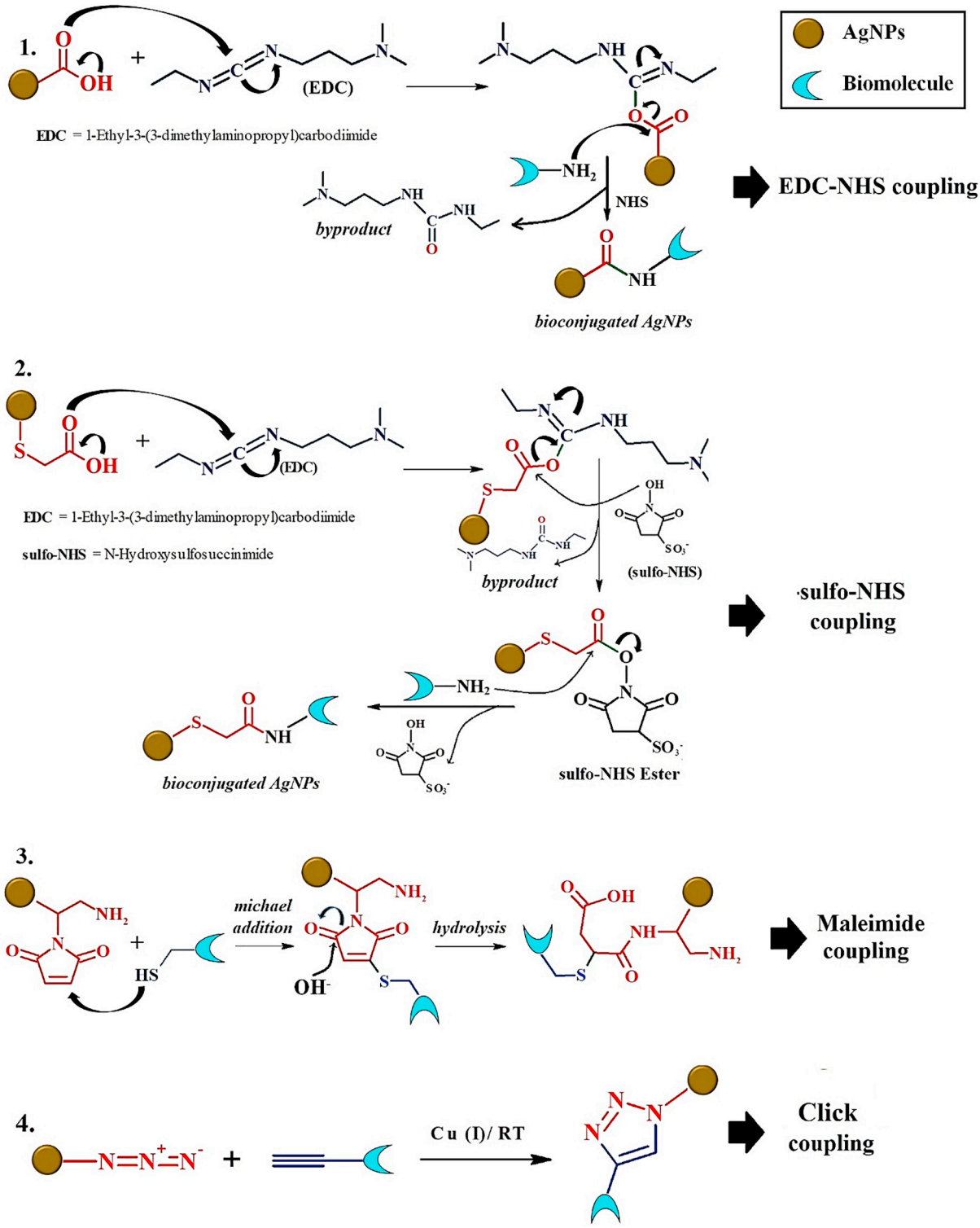

Fig. 3. Mechanism of bioconjugation of AgNPs

participating functionalized AgNPs and biomolecules do not require a preliminary chemical modification that may apparently lead to a loss of activity. Thirdly, the EDC mediated amide coupling favors an easy removal of the excess of reagents used and the byproducts by dialysis or gel-filtration [120]. The disadvantage of this method is that, the ester intermediate rapidly hydrolyses in aqueous solution due to which the reaction must occur swiftly. However, the stability of the active ester intermediate improves substantially in the presence of reagents, such as N-hydroxysuccinimide (NHS) or Nhydroxysulfoxuccinimide (sulfo-NHS) [121] (Fig. 3). Another disadvantage of EDC coupling involves the self-polymerization of participating biomolecule, specifically, a peptide that has both amine and carboxylic functionalities. It requires a persistent removal of the excess of reagent before conjugating it to functionalized AgNPs [122] to prevent the self-polymerization. However, the EDC-based amide coupling does not validate an oriented immobilization of biomolecules with higher structural complexity, such as antibodies due to the optimum incubation conditions required for the coupling that also includes a neutral pH, ionic strength and poor

aqueous stability of the ester intermediate. These physicochemical conditions only promote a direct covalent bonded immobilization of the most reactive amino groups of the antibody [123].

2.2.3. Azide-alkyne click chemistry for AgNPs bio-conjugation

Click chemistry presents nature-inspired reactions occurring under milder reactions for procuring high yields of easily purified final products in the physiologically benevolent solvents [124]. Over the past decades, click chemistry reactions presented profound clinical applications of which the *in-situ* synthesis of enzyme inhibitors presents the most recent development [125], which also validates considerable biocompatibility of these reactions for designing bio-conjugated nanopharmaceuticals. However, the azide-alkyne click cycloaddition approach for developing bio-conjugated AgNPs generally requires a tedious pre-synthesis of azide/ alkyne functionalized participating species [126]. In addition, this approach often suffers a low yield, thereby limiting its efficacy for nanoparticle bio-conjugation [127]. Though some reports revealed the synthesis of alkynyl-carboxyl AgNPs for conjugating to small molecule ligands such as ethanol, 4-(prop-2-ynyloxy) pyridine for colorimetric detection of cations [128]; however, the exhaustive accounts specifically on triazole-mediated bio-conjugation of AgNPs are not much available. Still, the click chemistry approach holds much promise in the contemporary silver-nanopharmaceutical paradigm. Fig. 3 demonstrates the mechanism of bioconjugation of AgNPs via recent approaches. Similarly, the coupling of hydrazide groups to the nanoparticle surface with aldehyde groups of the biomolecule [129] present another under-utilized bio-conjugation strategy for AgNPs. An oxidation of the surface hydroxyl groups in the presence of reagents sodium periodate [130] and galactose oxidase [131] generates an aldehyde group on biomolecules that generally do not possess an aldehyde functionality that may be conjugated to amine tagged AgNPs. However, the hydrazide coupling requires rigorous control of the ligand modification and suffers a very poor yield in the bio-conjugation process [132,133].

3. Clinical applications of bio-conjugated AgNPs

The aqueous stabilization or anchoring with appropriate biologically kind hydrophilic functionalities prepares the AgNPs for bio-conjugation with desired biomolecules. The bio-conjugated AgNPs present numerous applications for countering challenging clinical intricacies that are otherwise tedious to manage by the customary approaches [134–137]. The bio-conjugated AgNPs also present a robust candidature for the emerging clinical development paradigm such as next-generation antibiotics, drug delivery vehicles and anticancer theranostics [138–141]. The frequently employed peptides for therapeutic delivery of AgNPs comprise cell-penetrating TAT (trans-activating transcriptional activator) and TAT-like peptides [142], RGD (arginylglycylaspartic acid) responsible for cell adhesion to the extracellular matrix [143], cell-penetrating pep-I peptide that facilitates bio-delivery of molecules through the transmembrane pores thereby translocating the proteins into subcellular compartments [144], neuropeptides and the rabies virus-derived peptide. In addition, the natural antimicrobial peptides (AMPs) along with the small cationic peptides also present a suitable candidature in the peptide bio-conjugated AgNPs realm. This bio-conjugation not only mitigates the nanoparticle toxicity but also regulates their cellular uptake for an enhanced *in vivo* activity. The conjugation of functional peptides to AgNPs displays substantial applications in umpteen paradigms including drug delivery, cancer therapy, intracellular delivery, neurology and many others [145]. AgNPs reportedly display remarkable antimicrobial properties; however, the requirement of a higher effective concentration leading to cytotoxicity and ineffectual performance against multidrug-resistant (MDR) strains limits their antimicrobial application. Similarly, the nucleic acids stabilized AgNPs through their phosphate groups. Bio-conjugation, however, proceeds with a prior modification of the nucleotide with an alkanethiol group, preferably at the 5´ terminal that provides a superior bio-conjugation efficiency rather than the 3´ terminal of the tagged nucleotide [146]. Treatment of the thiol tagged nucleotide with reducing agents such as dithiothreitol, and tris(2-carboxyethyl)phosphine (TCEP) prevents the occurrence of side reactions such as disulfide formation thereby ensuring a free availability of the bio-conjugable functionalities [147,148]. In addition, the modification of oligonucleotides with multiple thiol-containing ligands such as triple cyclic disulphide, multiple thiols and thioctic acid [149] provide an additional stabilization due to enhanced metal-ligand interactions [150]. The AgNPs-nucleotide bio-conjugates play a key role in diagnostic applications and in the development of nano-theranostics due to a stress-free cellular transit of DNA functionalized nanomaterials than free single-stranded DNA. Likewise, the DNA template in situ formation of AgNPs also serves as effective drug vehicles.

3.1.1. Bio-conjugated AgNPs for targeting MDR microbes

The inherent antimicrobial potency of bioconjugated AgNPs resulting in microbial necrosis emanates principally because of the cellular oxidative stress, which further triggers a cascade of intracellular events eventually causing microbial mortality. Interestingly, the biofunctionalized AgNPs with biomacromolecules such as starch, cellulose, dextran function as antibiotic vehicles where the drug encapsulates in the biomacromolecule's cavity. Interestingly, biofunctionalized AgNPs reportedly target the microbial efflux pumps by modifying their expression or via complete suppression of activity, thereby displaying precedence over the representative antibiotics vulnerable to the microbial efflux [151]. Loading of antimicrobial peptides (AMPs) on AgNPs through a suitable linker molecule provides nanotherapeutic-systems with excellent potency for targeting MDR microbes [152]. AMPs possess significant clinical benefits such as a broad-spectrum potency, prompt inception of bioactivity, and relatively low occurrence of resistance. Still, the natural AMPs are vulnerable to the background environments, such as the presence of proteases, changes in pH in addition to the potential toxicity for oral application and uneconomical production costs. Upon bio-conjugation to AgNPs, the AMPs display brilliant synergistic biocidal effect against the target microbes with minimal toxicity. However, the development of new generation antimicrobials must consider the modulation of the microbial efflux pumps for an optimal activity [153]. The past decade witnessed tremendous developments in the designing of AgNP-AMP nano-bio conjugates for replacing several representative drugs susceptible to MDR phenomenon. Mohanty *et al.* (2013) investigated the antimicrobial potency of bio-conjugated AgNPs tagged to cationic antimicrobial peptides (AMPs) such as NK-2, LL-37 and LLKKK-18 against MDR strains of *Mycobacterium smegmatis* and *Mycobacterium marinum.* Reportedly, NK-2 and LLKKK-18 displayed a substantial synergistic effect with bioconjugated AgNPs at the concentration 0.5–1.0 ppm against *M. smegmatis*. These biogenic AgNPs also displayed substantial synergism with the antituberculosis drug rifampin against *M. smegmatis*. Importantly, the biogenic AMP loaded AgNPs exhibited no cytotoxicity or DNA damage on macrophages at the bactericidal dose; however, toxicity and micronuclei formation in cytokinesis-blocked cells appeared at higher doses of bio-conjugated AgNPs [154]. Avila *et al.* (2017) further confirmed the synergistic antimicrobial effect of AMPs on bio-conjugation with AgNPs against MDR strains of *Escherichia coli* and *Pseudomonas aeruginosa.*by investigating the synergistic oligodynamic effect of AMP Ubiquicidin (UBI) conjugated to AgNPs through -NH_2 group. A marked amplification in the antimicrobial effect appeared at a concentration of 75 μg/mL concentration due to a multimeric or polyvalent arrangement of ligands on the nanoparticle surface [155]. Pal *et al.* (2019) provided another validation for anti-MDR bactericidal potency of bio-conjugated AgNPs tagged with antimicrobial peptides (AMP): AY1 [FLPKLFAKITK-KNMAHIR], CAY1 [CFLPK LFAKITKKNMAHIR] and AY1C [FLPKLFAK-ITKKNMAHIRC], through a cysteine linker at their N- or C-terminal [156].

The AMPs experience a weak bonding with the nanosystems that result in their dynamic exchange from the nanoparticle surface while retaining the original conformation. The cysteine linked and AgNP-tagged AMPs displayed dynamic hydrophobic interactions with the acyl chains of phospholipid head groups or cell membrane. These interactions serve as driving force for their antimicrobial activity where the AMPs readily and reversibly detach from the AgNP surface by forming a pore in the microbial membrane [157]. These peptide-conjugated AgNPs served as favorable materials for targeting MDR strains of bacteria *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species* with a minimum inhibitory concentration (MIC) in the range 5–15 μM. In addition, the nano system demonstrated an antimicrobial activity higher than the combined antimicrobial activities of AgNPs and AMPs. Lambadi *et al.* (2015), bio-conjugated AgNPs with AMP polymyxin B and tested the potency of this nanosystem against MDR strains of *Vibrio fluvialis* and *P. aeruginosa*. The polymyxin capped AgNPs displayed a three-fold higher synergistic oligodynamic effect compared to the ordinary citrate-capped AgNPs with MIC = 4.5 μg/mL by inducing the morphological damage to the microbial membrane and by inhibiting the microbial biofilm formation. The bactericidal effect of this nanosystem also assisted in the removal of endotoxins from solutions, thereby mitigating the recalcitrant bacterial infections in patients with compromised immune system [158]. Chaudhary *et al.* (2016), tethered single-walled carbon-nanotubes (SWCNT) to AgNPs and bio-conjugated this system to AMP TP359 to investigate the antimicrobial potency of this system against both MDR gram-positive (*Staphylococcus aureus* and *Streptococcus pyogenes*) and MDR gram-negative pathogens (*Salmonella enterica serovar Typhimurium* and *Escherichia coli*). The conjugation exhibited an intense synergistic bactericidal effect of TP359 with SWCNTs-Ag. Much lower concentrations of the TP359 (0.3–0.08 μg/ml) and SWCNTs-Ag (7.8–1.9 μg/ml) displayed the anticipated antibacterial effect against the test strains as compared to the normal TP359 (MIC: 7.8–1.9 μg/ml) and SWCNTs-Ag (MIC: 125–62.5 μg/ml). Importantly, the nanosystem also displayed minimal cellular toxicity as tested on the murine macrophages and Hep2 cells at their MIC concentrations (5–2.5 μg/ml) [159]. Apart from natural AMPs appended to AgNPs, the small synthetic peptides appended to nano silver also present marked antimicrobial properties. Bajaj *et al.* (2018), provided the first report on antimicrobial AgNPs bio-conjugated with small cationic peptides: L-His-L-Arg-OMe and L-Arg-L-Arg-OMe; by using EDC/ NHS amide bond coupling chemistry with 2-mercaptopropanoic acid (MPA) as a cross-linker. The ligand exchange method enabled the tagging of MPA to citrate stabilized AgNPs. The –SH group of the linker molecule anchors to the AgNP surface and the free –COOH group participates in bio-conjugation with peptides. These conjugates demonstrated endurable cytotoxicity and significant antimicrobial activity against bacterial strains such as *E. coli*, *S. aureus* and fungal species *C. albicans*, *C. glabrata* with an IC50 in the range 24.16–50.83 μM. The FE-SEM investigations and time-kill assays validated the cell wall disruption mechanism for antimicrobial activity of peptide bio-conjugated AgNPs, with a potency superior to the non-conjugated AgNPs and commercial antimicrobials such as kanamycin and amphotericin B [160]. Syed *et al.* (2018), prepared silver nanoparticles conjugated with 2,4-Diacetylphloroglucinol (2,4 DAPG) and investigated the activity of the prepared bioconjugated nano-complex against phytopathogens and human pathogens. Reportedly, the bio-conjugated nano-complex exhibited significant activity against all the test pathogens, with the highest activity observed against Shigella flexneri (inhibition zone, 38.33 ± 0.33). In summary, the findings from the present study attribute to the development of nano-complex as a useful tool against MDR infections [161]. Bacteriocin produced by a probiotic strain of *Lactobacillus paracasei* presents a superior efficacy against a large number of MDR strains. In order to prevent the degradation of bacteriocin before reaching its target, Gomaa *et al.* (2019) prepared bacteriocin/AgNPs bio-conjugate. The results revealed that AgNPs conjugated with bacteriocin demonstrated enhanced antibacterial efficiency against MDR strains compared to bacteriocin or AgNPs alone [162].

3.1.2. Bio-conjugated AgNPs with anticancer properties

The emergence of biofunctionalized nanomaterials and the development of state of the art nanotheranostics has also revolutionized anticancer chemotherapy and diagnosis. The exceptional plasmonic properties of bio-conjugated AgNPs in addition to considerable biocompatibility and a superior bio-stability warrant their applications as nano-theranostics and bioimaging agents in clinical oncology and for addressing cancer-related complexities [163]. In addition, the AgNPs possess several intrinsic, clinically significant features such as targeting the cellular mitochondrial system leading to the production of ROS (reactive oxygen species), disruption of cellular ATP synthesis, instigating DNA damage and alteration of critical biological pathways required for the survival of cancer cells [164]. The cancer cell directed oxidative stress therapy, exhausting the cancer cells' ATP storehouse thereby damaging its central dogma are some of the desirable anticancer therapeutic effects manifested by AgNPs [165]. In addition, unlike the naked, colloidal stabilized AgNPs, the bioconjugated, surface engineered AgNPs conserve their unique surface plasmonic and optical properties useful for bioimaging of morbid cells and for developing diagnostic probes in anticancer therapy. [166]. Hence, the anticancer properties of bio-conjugated AgNPs require a comprehensive acknowledgement while addressing the next generation anticancer theranostics. Farkhani *et al.* (2017) reported significant augmentation in the anticancer activity of AgNPs biofunctionalized with cationic cell-penetrating peptides (CPP): [RW]3, [RW]4, [RW]5, [RW]6, R5W3R4 and R9. The CPPs that serve as intracellular transit vehicles [167] mainly comprise positively charged amino acid residues such as arginine and lysine [168]. EDC/NHS mediated amide bond coupling led to their bio-conjugation with AgNPs tagged with 2-mercaptopropanoic acid (MPA). The bioconjugation with CPPs lowered the negative potential of AgNP, hence reducing the electrostatic barrier of cell membrane for an easy transit of the drug into the cells. This eventually intensifies the instance of cell-particle interactions causing an enhanced cellular internalization of AgNPs, thereby raising their toxicity to the tumor cells [169]. The studies also suggested a superior antitumor activity for the CPP with tryptophan as a part of their sequence.

The efflux pumps in the cancer cells restrain the cellular internalization of therapeutics, adversely affecting the anticancer chemotherapy. Hence, the novel, new-generation theranostics must also ensure an effective bypassing of the active cellular efflux for an optimal drug activity. The CPP-modification presents the most efficient strategy for enhancing the intracellular delivery of AgNPs. Upon bio-conjugation, the bioactivity of CPP, that involves multiple pathways such as endocytosis, macropinocytosis, energy-independent translocation, and pore formation; couples with the intrinsic biocidal potency of AgNPs [170,171]. Liu *et al.* (2012) developed cell-penetrating peptide TAT (amino acid sequence of CGGGYGRKKRRQRRR) bio-conjugated AgNPs of mean size 8 nm, for targeting MDR cancer. The thiolated TAT peptide directly conjugates to the surface of AgNPs, forming a stable Ag-S bond thereby yielding AgNP-TAT nanopharmaceutical system that displayed commendable antitumor activity in both MDR susceptible and non-vulnerable cells. The failure of the cellular efflux to pump out the large-sized bio-conjugated AgNPs by 'size exclusion effect', contributed to the anti-MDR effect of the nano-bio conjugate. Interestingly, the AgNP-TAT conjugate displayed a 24-fold enhanced antitumor effect, superior to the commercial antitumor drug doxorubicin and compared to their non-functionalized counterparts. Specifically, the AgNP-TAT system effectively inhibited the tumor growth in the mice bearing malignant melanoma at a dose of 1 nmol/kg, compared with the effective dose (4.3 μmol/kg) of doxorubicin. The TAT-modification also contributed to mitigating the physiological toxicity associated with AgNPs [172]. In another study, Casañas Pimentel *et al.* (2016) prepared AgNPs conjugated with soybean agglutinin (SBA) and investigated their

cytotoxicity in non-cancerous (MCF 10A) and breast cancer cells (MDA-MB-231and MCF7). The findings of the study revealed that AgNPs bioconjugated with SBA showed similar cytotoxicity against the cancer cells, compared to the AgNPs [173]. The bioconjugated nanoparticle-based approach demonstrated commendable results, but still the heterogeneity of the tumor and its stroma pose considerable challenges for clinicians and nanotechnologists [174] to develop highly specific nanoformulations for selectively targeting the cancer cells. In addition, it also necessitates the consideration of critical parameters such as physiological barriers [175], limited carrying capacity, enhanced permeability and retention effect (EPR), variability of nanoparticles, and regulatory and manufacturing issues for commercializing the antitumor peptide conjugated AgNPs [176].

3.1.3. Bio-conjugated AgNPs with biosensing and diagnostic applications

Upon interacting with the characteristic dielectric constants of the metallic nanoparticles, the electromagnetic radiation induces collective oscillation of the surface conduction electrons referred to as surface plasmons of the illuminated nanoparticles [177]. This results into a localized enhancement of the electromagnetic field upon the excitation of the surface plasmons of the irradiated nanoparticles. The displacement of plasmonic electrons establishes an electrical dipole on the nanoparticle surface, thereby creating an additional electric field [178]. The net electric field on the nanoparticle surface depends on the electric field of the incident electromagnetic wave and that created by the plasmon electrons. Interestingly, the AgNPs possess a greater potency to support surface plasmonic resonance under visible radiation. The position of SPR band is highly localized and characteristic of the size of nanoparticle, and hence serve in bioanalytical fingerprinting [179].

The bio-conjugated AgNPs hold unique optical and plasmonic characteristics, along with physiological benevolence, an aspect advantageously exploited for biological probing, for developing diagnostic sensors and for the detection of biomarkers by immunoassays [180]. The localized surface plasmon resonance (LSPR) of AgNPs prompts the application of conjugated AgNPs in chemical and biological sensing. As compared to the other plasmonic nanomaterials, AgNPs possess a superior theoretical refractive index sensitivity (RIS) [181]. In addition, the spherical AgNPs exhibit a stronger and intense LSPR absorption peak at 400 nm compared to the other nano-metallic counterparts [182]. Interestingly, the bio-conjugated AgNPs enhance the immobilization of target detection molecules and reportedly enhance the performance of other electrochemical immunosensors [183]. The antibody functionalized AgNPs in combination with suitable separation methods also present fascinating applications for developing sensitive fluorescence detection system to detect biomarkers [184,185].

Lee *et al.* (2007) first reported on AgNPs bio-conjugated to cyclic-disulfide anchored oligonucleotide as diagnostic probes with enhanced stability in the adverse physicochemical environment and displayed extremely cooperative binding properties with intensely sharp melting transitions [186]. Likewise, Thompson *et al.* (2008) presented the first ever report of bio-conjugated nanoparticle-based DNA biosensors. Reportedly, the oligonucleotide-AgNPs conjugates function as diagnostic probes with a larger extinction coefficient for detecting a lower concentration of a specific DNA sequence. The investigations, however, did not assure PCR-less detection of genomic material; still the increased sensitivity for DNA detection prove useful for a variety of applications [187]. Liu *et al.* (2012) presented another report for highly sensitive, quantitative detection of HIV DNA. The sandwich hybridization of HIV DNA results in the aggregation of AgNPs leading to a plasmon coupling between close proximity nanoparticles, thereby altering the LSPR light scattering signals of AgNPs. The strong plasmon resonance scattering signals of the nanoconjugates hence form the basis of biosensing. The highly reproducible facile synthesis of DNA-AgNP conjugates takes place by incubating surfactant (FSN-100) stabilized AgNPs with thiolated DNA by the salt ageing method. Importantly, these bionano-conjugates apply in highly sensitive detection of low concentration (195 pmol L^{-1}) of a specific DNA sequence based on the LSPR light scattering signals of bio-conjugated AgNPs [188]. Pal *et al.* (2009) presented the first, clinically exploitable AgNPs conjugated to chimeric phosphorothioate modified DNA (ps-po-DNA) with superior stability in buffer conditions responsive to DNA hybridization. The nanoconjugates displayed multivalent Ag-S interaction between the surface of nanoparticles and the ps-domain of DNA. As a result, the remaining DNA sequence containing a recognition sequence with a normal phosphate backbone points away from the nanoparticle surface and undergoes hybridization with its complementary DNA. Moreover, the higher stability of these nanoconjugates in buffer solutions ensures their applications in nanophotonics and biosensing [189,190]. Further extending the DNA sensing application of bio-conjugated AgNPs, Lubitz *et al.* (2011) reported the biological properties of AgNPs with size 20 nm tethered to G-quadruplex DNA tagged with phosphorothioate anchor residues. The conjugates comprised of stacked G-tetrad plains that offered favorable conditions for an effective π overlapping, compared to the base pairs of the canonical double-stranded DNA. In addition, the bio-conjugated AgNP di/trimers displayed stronger and broader absorption spectra indicating a plasmonic coupling between the particles [191]. The bio-conjugated AgNPs also demonstrate useful applications in the sensitive detection of microbes. Abbaspour *et al.* (2014) described a sensitive and highly selective sandwich immunosensor based on AgNPs bioconjugated to dual-aptamers for the detection of gram-positive bacterium *Staphylococcus aureus.* In the reported bioassay, biotinylated primary anti- *S. aureus* aptamer served as a capture probe immobilized on streptavidin coated magnetic beads (MB). Alternately, the secondary anti- *S. aureus* aptamer conjugates to AgNPs for sensitive detection of the target. The Apt/*S. aureus*/apt-AgNP sandwich complex forms on the surface of magnetic beads in the presence of target bacterium, and the electrochemical signal of AgNPs followed through anodic stripping voltammetry. This reported electrochemical immunosensor displayed an extended dynamic range from 10 to 1106 cfu/mL with a low detection limit of 1.0 cfu/mL (S/N = 3). The high sensitivity of the assay validates potential applications for the trace detection of bacterium that is rather difficult with the representative methods [192]. Li *et al.* (2015) fabricated a multifunctional theranostic agent Ag-Sgc8-FAM for apoptosis-directed cancer therapy and fluorescence-enhanced cell imaging. The aptamer-silver conjugates (Ag-Sgc8, Ag-TDO5) readily internalize into the target cells by receptor-mediated endocytosis, and encourage the apoptosis of CCRF-CEM and Ramos cells, which further depended on the concentration of aptamer-AgNPs conjugates, and the incubation time between cells and the conjugate. Compared to the Sgc8-FAM molecules, the AgNPs bio-conjugated Sgc8-FAM served as an excellent imaging agent as numerous Sgc8-FAM molecules aggregate on the surface of AgNPs for multiple binding with CCRF-CEM cells and signal amplification. The aptamer-AgNPs conjugates displayed marked potential as theragnostic agents for inducing specific apoptosis of cells and in achieving the real-time cellular imaging [193]. Tang *et al.* (2015) developed DNA-templated bioconjugated AgNPs as two-photon excitation (TPE) based sensor for detecting GSH in live cells and tissues. The conjugates exhibited the anticipated two-photon-sensitized fluorescence properties, a superior cell permeability, high stability and biocompatibility, in addition to a robust, subtle, and selective profile for quantitative detection of GSH even under complex biological environment. Due to the association of GSH in mediating a variety of diseased conditions, the bio-conjugated DNA-AgNP probes hold great potential for *in vitro* and *in vivo* applications in anti-cancer drug screening, medical research and clinical diagnostics [194]. Sun *et al.* (2019) designed a unique, highly sensitive platform for the detection of DNA based on the DNA-templated silver nanoparticles (AgNPs) that prompt the signal amplification with electrochemical atom transfer radical polymerization. The biosensor displayed a detection limit of minimum 4.725 aM T-DNA under the optimal conditions and ATRP amplification, in addition to a highly sensitive detection of DNA in actual serum samples [195]. Nasirian *et al.* (2017) developed

Table 1
Recent cutting-edge patents on the application of bio-conjugated AgNPs

Biomolecule conjugating with AgNPs	Application	Patent no.	Ref.
Immunoglobulin G (IgG)	Analyte detection devices to detect minute quantities of a target bioanalytes such as pathogenic antigen or antibody in a sample	US10429383B2	[201]
DNA	Evaluation of the degree of damage to the DNA	CN109187446A	[202]
RNA	Specific detection of RNA sequences, selective differentiation between DNA and RNA by signal labelling and amplification	WO2019153137A1	[203]
Duplex RNA	Gene regulation, cellular delivery of RNA,	EP3335705A1	[204]
Enzyme (invertase) and antibody	Biomarkers for detection of antigens, abnormal kidney functioning and cancer	WO2018200829A1	[205]
DNA	Electrochemiluminescsensor sensor	CN108663354A	[206]
M13 virus	Biosensing of heavy metals	KR20190110247A	[207]
Enzymes: glucose oxidase, horseradish peroxidase, reductase	Biosensing or metabolites	WO2019139537A1	[208]
Fibronogen	Quantization of fibrinogen in blood	WO2019203486A1	[209]
Nucleic acids	Detection of aptamers and antibodies	US20190323069A1	[210]
Nucleotide sequence comprising a mutated portion of the mutation gene	Probes for detection of faulty genes	WO2019022385A1	[211]
Nucleotide sequence having a point mutation in codon 12 or 13 in exon 2 of KRAS	Single base mutation detection for predicting the responsiveness of the lung cancer patient to the drug.	KR101991593B1	[212]
Antibodies	Immunoassay for the detection of one or more species of infectious disease biomarker proteins	WO2018237227A1	[213]
Antibody	Assay for the detection of tenofovir	US20190025334A1	[214]
Nucleic acid molecule, such as phosphorothioate DNA	Molecular tags for biomarker and biosignature detection	US20190242887A1	[215]
Antibody	Nano-probes for detection of bioanalytes	CN108226477A	[216]

a fluorescence resonance energy transfer (FRET) - based nano-bioprobe based on-off signaling procedure to explain the selective detection of aflatoxin B1 (AFB1). An amino-modified aptamer against AFB1 was conjugated to fluorescent polymer dots, containing poly [(9,9-dioctyl-fluorenyl-2,7-diyl)-co-(1,4-benzothiadiazole)] as the fluorophore and the complementary DNA (cDNA) conjugated to AgNPs acting as FRET acceptors. In the absence of AFB1, the aptamer and its cDNA conjugate to form (aptamer-cDNA) complex in a suitable solution thereby bringing the polymer dots near AgNPs resulting in FRET from the donor to the acceptor due to spectral overlap between the emission of the polymer dots and the absorption of the AgNPs. Eventually, it shuts-off the fluorescence of the polymer dots probe. Contrarily, the presence of AFB1 leads to the release of the aptamer from the cDNA-AgNP aggregate resulting in a significant fluorescence recovery. These nano-conjugates successfully detected AFB1 with a detection limit 0.3 pg/mL, in close agreement with the results obtained from established enzyme immunoassays [196]. Kurdekar *et al.* (2017) investigated the application of fluorescent AgNPS bioconjugated with streptavidin for early detection of HIV infection. The group performed fluorescence-based sandwich immunoassay in clinical specimens to detect HIV-1 p24 antigen, profusely present in the early stages of HIV infection. The results indicated that fluorescent silver nanoparticle-based immunoassay could detect HIV-1 p24 antigen with high sensitivity and specificity, with a detection range between 10 and 1000 pg mL^{-1} [197]. Khristunova *et al.* (2019) developed an electrochemical immunosensor based on the antibody-AgNPs bioconjugation for the sensitive detection of antibodies to tick-borne encephalitis virus in the concentration range from 50 to 1600 IU mL^{-1}, with a detection limit of 50 IU mL^{-1}. [198]. Boca-Farcau *et al.* (2014) developed chitosan AgNPs labeled with a p-amino-thiophenol Raman reporter molecule. The prepared nanoparticles were further bioconjugated with folic acid (FA). Darkfield microscopy and scattering spectra of the particles inside the cells confirmed the targeted uptake of the FA conjugated AgNPs by human ovarian cancer cells. Moreover, the targeted photothermal treatment of cells loaded with nanoparticles by continuous wave-near-infrared laser displayed an effective therapeutic response [199]. In another study, Yen *et al.* (2015) developed a rapid point-of-care (POC) diagnostic device by utilizing the optical properties of AgNPs for the diagnosis of ebolaviruses, dengue, and yellow fever via bio-conjugation of AgNPs with monoclonal antibodies that bind to specific biomarkers, where a rapid distinguishing the color of the test lines makes it possible to distinguish different biomarkers [200].

Table 1 presents the recent, cutting-edge inventions on bioconjugated AgNPs with applications ranging from the development of enzyme-immunoassays for the detection of antibody/ antigen, and bioanalytes to the development of AgNPs based bionano-probes for identifying erroneous genes and their expression.

4. Conclusion and future perspectives

Conjugation of AgNPs with biomolecules of interest present exciting applications in the contemporary era that include the development of biocompatible nanopharmaceutics, effective drug delivery vehicles, colorimetric biosensors/ bio-analyzers and the next-generation antibiotics and theranostics. The nano-bio conjugation prototype also presents an effective phasing out of the biologically and environmentally harsh agents and molecules without any subsequent loss of the activity. AgNPs, a widely exploited nanomaterial for its brilliant plasmonic, biological and optoelectronic properties present a robust candidature as the forefront material for the future pharmaceutical realm with wide spread applications ranging from the development of nano-therapeutics targeting multidrug-resistant microbes to the discovery of nano-theranostics for effective treatment of cancerous conditions. However, unlike the existing organo-chemicals, the efficiency and scaling up of the bio-conjugated AgNPs, understanding their physiological and environmental metabolism, their live interactions and outcomes with various ecosystems still need to be addressed before accepting them as materials of the future.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

Acknowledgement

PP thanks the Department of Chemistry, University of Petroleum & Energy Studies (UPES), MS thanks the Department of Chemistry, Uttaranchal University (UU), HM thanks the Department of Chemistry, Lovely Professional University (LPU) for providing the necessary resources. The authors duly acknowledge Department of Chemistry, Guru Nanak Dev University (GNDU) for providing requisite resources for completing this work. GG, AKS, DK, DNK thanks Department of Pharmacy, Shoolini University for resources. DKC thanks IMU, Malaysia for research infrastructure. MMT and KD thanks

Ulster University and University of Technology Sydney for providing research facilities.

References

[1] a.P. Prasher, M. Singh, H. Mudila, Silver nanoparticles as antimicrobial therapeutics: Current perspectives and future challenges, 3Biotech 8 (2018) 411 b. P. Prasher, M. Singh, H. Mudila, Oligodynamic effect of silver nanoparticles: A review. BioNanoScience. 8 (2018) 951-962.

[2] J. Pulit-Prociak, M. Banach, Silver nanoparticles - a material of the future…? Open Chem. 14 (2016) 76–91.

[3] P. Prasher, M. Singh, H. Mudila, Green Synthesis of Silver Nanoparticles and their antifungal properties, BioNanoScience. 8 (2018) 254–263.

[4] S. Song, Y. Qin, Y. He, Q. Huang, C. Fan, H.-Y. Chen, Functional nanoprobes for ultrasensitive detection of biomolecules, Chem. Soc. Rev. 39 (2010) 4234–4243.

[5] S.A. Jadhav, H.B. Garud, A.H. Patil, G.D. Patil, C.R. Patil, T.D. Dongale, P.S. Patil, Recent advancements in silica nanoparticles based technologies for removal of dyes from water, Colloid. Interface Sci. Commun. 30 (2019) Article 100181.

[6] K. Liu, S. Qu, X. Zhang, F. Tan, Z. Wang, Improved photovoltaic performance of silicon nanowire/organic hybrid solar cells by incorporating silver nanoparticles, Nanoscale Res. Lett. 8 (2013) 88.

[7] J. Jimenez-Lamana, F. Laborda, E. Bolea, et al., An insight into silver nanoparticles bioavailability in rats, Metallomics. 6 (2014) 2242–2249.

[8] M. Mosavinia, T. Kikhavani, M. Tanzifi, M.T. Yaraki, P. Tajbakhsh, A. Lajevardi, Facile green synthesis of silver nanoparticles using Crocus Haussknechtii Bois bulb extract: Catalytic activity and antibacterial properties, Colloid. Interface Sci. Commun. 33 (2019) Article 100211.

[9] O.T. Jemilugba, E.H.M. Sakho, S. Parani, V. Mavumengwana, O.S. Oluwafemi, Green synthesis of silver nanoparticles using Combretum erythrophyllum leaves and its antibacterial activities, Colloid. Interface Sci. Commun. 31 (2019) Article100191.

[10] T.M. Pereira, V.L.P. Polez, M.H. Sousa, L.P. Silva, Modulating physical, chemical, and biological properties of silver nanoparticles obtained by green synthesis using different parts of the tree *Handroanthus heptaphyllus* (Vell.) Mattos, Colloid. Interface Sci. Commun. 34 (2020) Article 100224.

[11] R. Augustine, N. Kalarikkal, S. Thomas, Electrospun PCL membranes incorporated with biosynthesized silver nanoparticles as antibacterial wound dressings, Appl. Nanosci. 6 (2016) 337–344.

[12] A. Masri, A. Anwar, D. Ahmed, R.B. Siddiqui, M.R. Shah, N.A. Khan, Silver nanoparticle conjugation-enhanced antibacterial efficacy of clinically approved drugs cephradine and vildagliptin, Antibiotics (Basel.) 7 (2018) Article 100.

[13] T. Zhang, L. Wang, Q. Chen, C. Chen, Cytotoxic potential of silver nanoparticles, Yonsei Med. J. 55 (2014) 282–291.

[14] S.B. Gunnarsson, K. Bernfur, A. Mikkelsen, T. Cedervall, Analysis of nanoparticle biomolecule complexes, Nanoscale. 10 (2018) 4246–4257.

[15] J. Duran, C.P. Silveira, M. Duran, D.S.T. Martinez, Silver nanoparticle protein corona and toxicity: a mini review, J. Nanobiotechnol. 13 (2015) 55.

[16] J.S. Gebauer, M. Malissek, S. Simon, S.K. Knauer, M. Maskos, R.H. Stauber, W. Peukert, L. Treuel, Impact of the nanoparticle-protein corona on colloidal stability and protein structure, Langmuir. 28 (2012) 9673–9679.

[17] H. Huang, W. Lai, M. Cui, L. Liang, Y. Lin, Q. Fang, Y. Liu, L. Xie, An evaluation of blood compatibility of silver nanoparticles, Sci. Rep. 6 (2016) 25518.

[18] S. Juling, A. Niedzwiecka, L. Bohmert, D. Lichtenstein, S. Selve, A. Braeuning, A.F. Thunemann, E. Krause, A. Lampen, Protein corona analysis of silver nanoparticles links to their cellular effects, J. Proteome Res. 16 (2017) 4020–4034.

[19] S. Marin, G.M. Vlaseanu, R.E. Tiplea, I.R. Bucur, M. Lemnaru, M.M. Marin, A.M. Grumezescu, Applications and toxicity of silver nanoparticles: A recent review, Curr. Top. Med. Chem. 15 (2015) 1596–1604.

[20] L. Mei, Z. Lu, W. Zhang, Z. Wu, X. Zhang, Y. Wang, Y. Luo, C. Li, Y. Jia, Bioconjugated nanoparticles for attachment and penetration into pathogenic bacteria, Biomaterials. 34 (2013) 10328–10337.

[21] A. Borowik, K. Butowska, K. Konkel, R. Banasiuk, N. Derewonko, D. Wyrzykowski, M. Davydenko, V. Cherepanov, V. Styopkin, Y. Prylutskyy, P. Pohel, A. Krolicka, J. Piosik, The impact of surface functionalization on the biophysical properties of silver nanoparticles, Nanomaterials (Basel). 9 (2019) 973.

[22] O. A-C Burdusel, A.M. Gherasim, L. Grumezescu, A. Mogoanta, E.A. Ficai, Biomedical applications of silver nanoparticles: An up-to-date overview, Nanomaterials (Basel). 8 (2018) 681.

[23] M. Jha, N.G. Shimpi, Spherical nanosilver: Bio-inspired green synthesis, characterization, and catalytic applications, Nano-Struct. Nano-Objects. 16 (2018) 234–249.

[24] J.H. Shannahan, X. Lai, P.C. Ke, R. Podila, J.M. Brown, F.A. Witzmann, Silver nanoparticle protein corona composition in cell culture media, PLoS One 8 (2013) e74001.

[25] A.M. Bannunah, D. Vllasaliu, J. Lord, S. Stolnik, Mechanisms of nanoparticle internalization and transport across an intestinal epithelial cell model: Effect of size and surface charge, Mol. Pharm. 11 (2014) 4363–4373.

[26] P.K. Alla, P.K. Lauf, I. Pavel, A. Paluri, M. Marcopoulos, J. Yaklic, N.C. Adragna, Internalized silver nanoparticles alter ion transport and hemoglobin spectrum in human red blood cells, FASEB J. 30 (2016) Ib620.

[27] X.-F. Zhang, W. Shen, S. Gurunathan, Silver nanoparticle-mediated cellular responses in various cell lines: An *in vitro* model, Int. J. Mol. Sci. 17 (2016) 1603.

[28] H. Haase, A. Fahmi, B. Mahltig, Impact of silver nanoparticles and silver ions on innate immune cells, J. Biomed. Nanotechnol. 10 (2014) 1146–1156.

[29] L.Z. Flores-Lopez, H. Espinoza-Gomez, R. Somanathan, Silver nanoparticles: Electron transfer, reactive oxygen species, oxidative stress, beneficial and toxicological effects. Mini review, J. Appl. Toxicol. 39 (2019) 16–26.

[30] K. Urbanska, B. Pajak, A. Orzechowski, J. Sokolowska, M. Grodzik, E. Sawosz, M. Szmidt, P. Sysa, The effect of silver nanoparticles (AgNPs) on proliferation and apoptosis of *in ovo* cultured glioblastoma multiforme (GBM) cells, Nanoscale Res. Lett. 10 (2015) 98.

[31] J.S. Gebauer, M. Malissek, S. Simon, S.K. Knauer, R.H. Stauber, W. Peukert, L. Treuel, Impact of the nanoparticle–protein corona on colloidal stability and protein structure, Langmuir. 28 (2012) 9673–9679.

[32] V.A. Litvin, B.F. Minaev, G.V. Baryshnikov, Experimental and theoretical study of the mechanism formation of silver nanoclusters in the reduction reaction of Ag^+ ions by alizarin solution, Colloid. Interface Sci. Commun. 29 (2019) 47–54.

[33] L. Guerrini, R.A. Alvarez-Puebla, N. Pazos-Perez, Surface modifications of nanoparticles for stability in biological fluids, Materials (Basel). 6 (2018) 1154.

[34] F. Benyettou, R. Rezgui, F. Ravaux, T. Jaber, K. Blumer, M. Jouiad, L. Motte, C. J-C Olsen, M. Platas-Iglesias, A. Trabolski Magzoub, Synthesis of silver nanoparticles for the dual delivery of doxorubicin and alendronate to cancer cells, J. Mat. Chem. B. 3 (2015) 7237–7245.

[35] J.K. Patra, G. Das, L.F. Fraceto, et al., Nano based drug delivery systems: recent developments and future prospects, J. Nanobiotechnol. 16 (2018) 71.

[36] M.-A. Neouze, U. Schubert, Surface modification and functionalization of metal and metal oxide nanoparticles by organic ligands, Monatshefte Chem. Chem. Mon. 139 (2008) 183–195.

[37] H. Takekuma, K. Tagomori, S. Shinohara, S. Masuda, Y. Xu, Y. Chan, P. Wang, S. Ryuzaki, K. Okamoto, K. Tamada, How to make microscale pores on a self-assembled Ag nanoparticle monolayer, Colloid. Interface Sci. Commun. 30 (2019) Article 100175.

[38] S. Shankar, J. Chorachoo, L. Jaiswal, S.P. Voravuthikunchai, Effect of reducing agent concentrations and temperature on characteristics and antimicrobial activity of silver nanoparticles, Mater. Lett. 137 (2014) 160–163.

[39] H.D. Beyene, A.A. Werkneh, H.K. Bezabh, T.G. Ambaye, Synthesis paradigm and applications of silver nanoparticles (AgNPs), a review, Sustain. Mater. Technol. 13 (2017) 18–23.

[40] I. Fratoddi, Hydrophobic and hydrophilic Au and Ag nanoparticles. Breakthroughs and perspectives, Nanomaterials. 8 (2018) 11.

[41] M. Yamamoto, Y. Kashiwagi, M. Nakamoto, Size-controlled synthesis of monodispersed silver nanoparticles capped by long-chain alkyl carboxylates from silver carboxylate and tertiary amine, Langmuir. 22 (2006) 8581–8586.

[42] S.B. Vasanth, G.A. Kurian, Toxicity evaluation of silver nanoparticles synthesized by chemical and green route in different experimental models, Artif. Cells Nanomed. Biotechnol. 45 (2017) 1721–1727.

[43] A. Sukhanova, S. Bozrova, P. Sokolov, M. Berestovoy, A. Karaulov, I. Nabiev, Dependence of nanoparticle toxicity on their physical and chemical properties, Nanoscale Res. Lett. 13 (2018) 44.

[44] J.V.M. Giron, R.V. Vico, B. Maggio, E. Zelaya, A. Rubert, G. Benitez, R.C. Salvarezza, M.E. Vela, Role of the capping agent in the interaction of hydrophilic Ag nanoparticles with DMPC as a model biomembrane, Environ. Sci. Nano. 3 (2016) 462–472.

[45] R. Behra, L. Sigg, M.J.D. Clift, F. Herzog, M. Minghetti, B. Johnston, A. Petri-Fink, B. Rothen-Rutishauser, Bioavailability of silver nanoparticles and ions: From a chemical and biochemical perspective, J. R. Soc. Interface. 10 (2013) 20130396.

[46] M.S. Selim, H. Yang, F.Q. Wang, X. Li, Y. Huang, N.A. Fatthallah, Silicone/Ag@SiO2 core–shell nanocomposite as a self-cleaning antifouling coating material, RSC Adv. 8 (2018) 9910–9921.

[47] L. Li, B. Li, J. Dong, J. Zhang, Roles of silanes and silicones in forming superhydrophobic and superoleophobic materials, J. Mater. Chem. A. 4 (2016) 13677–13725.

[48] D. Moore, J.R. Morber, R.L. Snyder, Z.L. Wang, Growth of ultralong ZnS/SiO_2 core−shell nanowires by volume and surface diffusion VLS process, J. Phys. Chem. C. 112 (2008) 2895–2903.

[49] J.V. Alimunnisa, K. Ravichandran, K.S. Meena, Synthesis and characterization of Ag@SiO2 core-shell nanoparticles for antibacterial and environmental applications, J. Mol. Liq. 231 (2017) 281–287.

[50] R. Liu, R.D. Priestley, Rational design and fabrication of core–shell nanoparticles through a one-step/pot strategy, J. Mater. Chem. A. 4 (2016) 6680–6692.

[51] S. Li, X. Jiao, H. Yang, Hydrophobic core/hydrophilic shell structured mesoporous silica nanospheres: Enhanced adsorption of organic compounds from water, Langmuir 29 (2013) 1228–1237.

[52] K. Nischala, T.N. Rao, N. Hebalkar, Silica-silver core-shell particles for antibacterial textile application, Colloids Surf., B. 82 (2011) 203–208.

[53] Y. Zhang, X. Kong, B. Xue, Q. Zeng, X. Liu, L. Tu, K. Liu, H. Zhang, A versatile synthesis route for metal@SiO_2 core–shell nanoparticles using 11-mercaptoundecanoic acid as primer, J. Mater. Chem C. 1 (2013) 6355–6363.

[54] L.Q. Xu, B.S.M. Yap, R. Wang, K.-G. Neoh, E.-T. Kang, G.D. Fu, Catecholamine-induced electroless metallization of silver on silica@polymer hybrid nanospheres and their catalytic applications, Ind. Eng. Chem. Res. 53 (2014) 3116–3124.

[55] L. Han, H. Wei, B. Tu, D. Zhao, A facile one-pot synthesis of uniform core–shell silver nanoparticle@mesoporous silica nanospheres, Chem. Commun. 47 (2011) 8536–8538.

[56] E. Ertem, B. Gutt, F. Zuber, S. Allegri, B.L. Ouay, S. Mefti, K. Formentin, F. Stellaci, Q. Ren, Core−shell silver nanoparticles in endodontic disinfection solutions enable long-term antimicrobial effect on oral biofilms, ACS Appl. Mater. Interfaces. 9 (2017) 34762–34772.

[57] P.C. Pandey, G. Pandey, One-pot two-step rapid synthesis of 3-aminopropyltrimethoxysilane-mediated highly catalytic Ag@(PdAu) trimetallic nanoparticles,

Catal. Sci. Technol. 6 (2016) 3911–3917.
[58] Z. Li, L. Jia, Y. Li, T. He, X.-M. Li, Ammonia-free preparation of Ag@SiO_2core/shell nanoparticles, Appl. Surf. Sci. 345 (2015) 122–126.
[59] D.V. Viazmitinov, L.B. Matyushkin, A.I. Maximov, Synthesis of core-shell Ag/SiO2 nanoparticles for SPASER structures, J. Phys. Conf. Ser. 541 (2014) 012015.
[60] S.G. Hernandez-Leon, J. Andre-i Sarabia-Sainz, G. Ramos-Clamont Montfort, A.M. Guzman-Partida, M. del Refugio Robles-Burgueño, L. Vazquez-Moreno, Novel synthesis of core-shell silica nanoparticles for the capture of low molecular weight proteins and peptides, Molecules 22 (2017) 22101712.
[61] I. Venditti, G. Testa, F. Sciubba, L. Carlini, F. Porcaro, C. Meneghini, S. Mobilio, C. Battocchio, I. Fratoddi, Hydrophilic metal nanoparticles functionalized by 2-diethylaminoethanethiol: A close look at the metal–ligand interaction and interface chemical structure, J. Phys. Chem. C. 121 (2017) 8002–8013.
[62] A. Fernandez-Lodeiro, J. Fernandez-Lodeiro, C. Nunez, R. Bastida, J.L. Capelo, C. Lodeiro, Polyamine ligand-mediated self-assembly of gold and silver nanoparticles into chainlike structures in aqueous solution: Towards new nanostructured chemosensors, ChemistryOpen. 2 (2013) 200–207.
[63] A. Andrieux-Ledier, B. Tremblay, A. Courty, Synthesis of silver nanoparticles using different silver phosphine precursors: Formation mechanism and size control, J. Phys. Chem. C. 117 (2013) 14850–14857.
[64] O. Sambalova, K. Thorwarth, N.B. Heeb, D. Bleiner, Y. Zhang, A. Borgschulte, A. Kroll, Carboxylate functional groups mediate interaction with silver nanoparticles in biofilm matrix, ACS Omega. 3 (2018) 724–733.
[65] C. Battocchio, C. Meneghini, I. Fratoddi, I. Venditti, M.V. Russo, G. Aquilanti, C. Maurizio, F. Bondino, R. Matassa, M. Rossi, S. Mobilio, G. Polzonetti, Silver nanoparticles stabilized with thiols: A close look at the local chemistry and chemical structure, J. Phys. Chem. C. 116 (2012) 19571–19578.
[66] R.A. Sperling, W.J. Parak, Surface modification, functionalization and bio-conjugation of colloidal inorganic nanoparticles, Phil. Trans. R. Soc. A. 368 (2010) 1333–1383.
[67] A.M. El Badawy, T.P. Luxton, R.G. Silva, K.G. Scheckel, M.T. Suidan, T.M. Tolaymat, Impact of environmental conditions (pH, ionic strength, and electrolyte type) on the surface charge and aggregation of silver nanoparticles suspensions, Environ. Sci. Technol. 44 (2010) 1260–1266.
[68] M. Tejamaya, I. Romer, R.C. Merrifield, J.R. Lead, Stability of citrate, PVP, and PEG coated silver nanoparticles in ecotoxicology media, Environ. Sci. Technol. 46 (2012) 7011–7017.
[69] L. Pinzaru, D. Coricovac, C. Dehelean, M. E-A Moaca, F. Mioc, I. Baderca, S. Sizemore, D. Brittle, C.D. Marti, A.M. Calina, C.S. Tsatsakis, Stable PEG-coated silver nanoparticles - A comprehensive toxicological profile, Food Chem. Toxicol. 111 (2018) 546–556.
[70] M. Xu, J. Liu, X. Xu, S. Liu, F. Peterka, Y. Ren, X. Zhu, Synthesis and comparative biological properties of Ag-PEG nanoparticles with tunable morphologies from janus to multi-core shell structure, Materials (Basel). 11 (2018) 1787.
[71] T. Pellegrino, L. Manna, S. Kudera, T. Liedl, D. Koktysh, A.L. Rogach, S. Keller, J. Radler, G. Natile, W.J. Parak, Hydrophobic nanocrystals coated with an amphiphilic polymer shell: A general route to water soluble nanocrystals, Nano Lett. 4 (2004) 703–707.
[72] L. Quaroni, G. Chumanov, Preparation of polymer-coated functionalized silver nanoparticles, J. Am. Chem. Soc. 121 (1999) 10642–10643.
[73] S. Sur, A. Rathore, V. Dave, K.R. Reddy, R.S.V. Sadhu, Recent developments in functionalized polymer nanoparticles for efficient drug delivery system, Nano-Struct. Nano-Objects 20 (2019) Article 100397.
[74] S. Ortelli, A.L. Costa, Nanoencapsulation techniques as a safer by (molecular) design tool, Nano Struct. Nano-Objects. 13 (2018) 155–162.
[75] K. Werengowska-Ciecwierz, M. Wisniewski, A.P. Terzyk, S. Furmaniak, The chemistry of bio-conjugation in nanoparticles-based drug delivery system, Adv. Cond. Matter Phys 2015 (2015) Article ID 198175.
[76] A. Ravindran, P. Chandran, S.S. Khan, Biofunctionalized silver nanoparticles: Advances and prospects, Colloids Surf. B. 105 (2013) 342–352.
[77] E. Ruckenstein, Z.F. Li, Surface modification and functionalization through the self-assembled monolayer and graft polymerization, Adv. Colloid Interface Sci. 113 (2005) 43–63.
[78] R. Gref, P. Couvreur, G. Barratt, E. Mysiakine, Surface-engineered nanoparticles for multiple ligand coupling, Biomaterials 24 (2003) 4529.
[79] R. Subbiah, S.B. Jeon, K. Park, S.J. Ahn, K. Yun, Investigation of cellular responses upon interaction with silver nanoparticles, Int. J. Nanomed. 10 (2015) 191–201.
[80] X.-F. Zhang, Z.-G. Liu, W. Shen, S. Gurunathan, Silver nanoparticles: Synthesis, characterization, properties, applications, and therapeutic approaches, Int. J. Mol. Sci. 17 (2016) 1534.
[81] H. Poblete, A. Agarwal, S.S. Thomas, C. Bohne, Understanding the interaction between biomolecules and silver nanoparticles, Biophys. J. 110 (2016) 341a.
[82] M. Marchioni, T. Gallon, I. Worms, P.-H. Jouneau, C. Lebrun, G. Veronesi, D. Truffier-Boutry, E. Mintz, P. Delangle, A. Deniaud, I. Michaud-Soret, Insights into polythiol-assisted AgNP dissolution induced by bio-relevant molecules, Environ. Sci. Nano. 5 (2018) 1911–1920.
[83] H.S. Toh, C. Batchelor-McAuley, K. Tschulik, R.G. Compton, Chemical interactions between silver nanoparticles and thiols:Aa comparison of mercaptohexanol against cysteine, Sci. China Chem. 57 (2014) 1199–1210.
[84] K.M. Vargas, Y.-S. Shon, Hybrid lipid–nanoparticle complexes for biomedical applications, J. Mater. Chem. B. 7 (2019) 695–708.
[85] J. Rademann, Chemoselective and bioorthogonal ligation reactions. concepts and applications, in: W. Russ Algar, Philip Dawson, Igor L. Medintz (Eds.), Angewandte Chemie International Edition. 57, 1 2017, https://doi.org/10.1002/anie.201710401.
[86] Y. Liu, H. Miyoshi, M. Nakamura, Nanomedicine for drug delivery and imaging: a promising avenue for cancer therapy and diagnosis using targeted functional nanoparticles, Int. J. Cancer. 120 (2007) 2527–2537.
[87] K.E. Sapsford, W.R. Algar, L. Berti, K.B. Gemmill, B.J. Casey, E. Oh, M.H. Stewart, I.L. Medintz, Functionalizing nanoparticles with biological molecules: Developing chemistries that facilitate nanotechnology, Chem. Rev. 113 (2013) 1904–2074.
[88] H.S. Jiang, Y. Zhang, Z.W. Lu, R. Lebrun, B. Gontero, W. Li, Interaction between silver nanoparticles and two dehydrogenases: Role of thiol groups, Small. 15 (2019) 1900860.
[89] L.S.B. Upadhyay, N. Verma, Synthesis and characterization of cysteine functionalized silver nanoparticles for biomolecule immobilization, Bioprocess Biosyst. Eng. 37 (2014) 2139–2148.
[90] K. Siriwardana, A. Wang, M. Gadogbe, W.E. Collier, N.C. Fitzkee, D. Zhang, Studying the effects of cysteine residues on protein interactions with silver nanoparticles, J. Phys. Chem. C 119 (2015) 2910–2916.
[91] Y.M. Go, J.D. Chandler, D.P. Jones, The cysteine proteome, Free Radical Biol. Med. 84 (2015) 227–245.
[92] G.J. Bartlett, C.T. Porter, N. Borkakoti, J.M. Thornton, Analysis of catalytic residues in enzyme active sites, J. Mol. Biol. 324 (2002) 105–121.
[93] A. Käkinen, F. Ding, P. Chen, M. Mortimer, A. Kahru, P.C. Ke, Interaction of firefly luciferase and silver nanoparticles and its impact on enzyme activity, Nanotechnology. 24 (2013) 345101.
[94] S. Mohr, H. Hallak, A. de Boitte, E.G. Lapetina, B. Brune, Nitric oxide-induced *S*-glutathionylation and inactivation of glyceraldehyde-3-phosphate dehydrogenase, J. Biol. Chem. 274 (1999) 9427.
[95] K.W. Fan, A.M. Granville, Surface property modification of silver nanoparticles with dopamine-functionalized poly(pentafluorostyrene) via RAFT polymerization, Polymers. 8 (2016) 81.
[96] N. Sui, L. Wang, F. Xie, F. Liu, H. Xiao, M. Liu, W.W. Yu, Ultrasensitive aptamer-based thrombin assay based on metal enhanced fluorescence resonance energy transfer, Microchim. Acta. 183 (2016) 1563–1570.
[97] C. Wei, X. Liu, Y. Gao, Y. Wu, X. Guo, Y. Ying, Y. Wen, H. Yang, Thiol–disulfide exchange reaction for cellular glutathione detection with surface-enhanced Raman scattering, Anal. Chem. 90 (2018) 11333–11339.
[98] A. Ghavidast, N.O. Mahmoodi, M.A. Zanjanchi, Synthesis and photochromic properties of disulfide-1,3-diazabicyclo[3.1.0]hex-3-ene functionalized silver nanoparticles, J. Mol. Liq. 198 (2014) 128–133.
[99] M. Sampath, S. Balasubramanian, Synthesis and characterization of silver bio-conjugates derived from DNA, J. Comput. Theor. Nanosci. 16 (2012) 284–291.
[100] Z. Matharu, A.J. Bandodkar, V. Gupta, B.D. Malhotra, Fundamentals and application of ordered molecular assemblies to affinity biosensing, Chem. Soc. Rev. 41 (2012) 1363–1402.
[101] J.M.J.M. Ravasco, H. Faustino, A. Trindade, P.M.P. Gois, Bio-conjugation with maleimides: A useful tool for chemical biology, Chem. Eur. J. 25 (2019) 43–59.
[102] P. Akkapeddi, A.M.F. S-A Azizi, et al., Construction of homogeneous antibody-drug conjugates using site-selective protein chemistry, Chem. Sci. 7 (2016) 2954–2963.
[103] J.M. Gorham, A.B. Rohlfing, K.A. Lippa, R.I. MacCuspie, A. Hemmati, R.D. Holbrook, Storage wars: How citrate-capped silver nanoparticle suspensions are affected by not-so-trivial decisions, J. Nanopart. Res. 16 (2014) 2339.
[104] L. Salvioni, E. Galbiati, et al., Negatively charged silver nanoparticles with potent antibacterial activity and reduced toxicity for pharmaceutical preparations, Int. J. Nanomed. 12 (2017) 2517–2530.
[105] K. Park, G. Tuttle, F. Sinche, S.L. Harper, Stability of citrate-capped silver nanoparticles in exposure media and their effects on the development of embryonic zebrafish (*Danio rerio*), Arch. Pharm. Res. 36 (2013) 125–133.
[106] B.H. Jun, W.Y. Rho, Silver nano/microparticles: Modification and applications, Int. J. Mol. Sci. (2019), https://doi.org/10.3390/books978-3-03921-178-4 MDPI books.
[107] L.R. Pokhrel, C.P. Andersen, P.T. Rygiewicz, M.G. Johnson, Preferential interaction of Na^+ over K^+ with carboxylate-functionalized silver nanoparticles, Sci. Total Environ. 490 (2014) 11–18.
[108] S. Tan, M. Erol, A. Attygalle, H. Du, S. Sukhishvili, Synthesis of positively charged silver nanoparticles via photoreduction of $AgNO_3$ in branched polyethyleneimine/HEPES solutions, Langmuir. 23 (2007) 9836–9843.
[109] Z. Liu, Y. Wang, Y. Zu, et al., Synthesis of polyethylenimine (PEI) functionalized silver nanoparticles by a hydrothermal method and their antibacterial activity study, Mater. Sci. Eng. C. 42 (2014) 31–37.
[110] L.-G.H. Y-M Long, X.-T. Yan, et al., Surface ligand controls silver ion release of nanosilver and its antibacterial activity against *Escherichia coli*, Int. J. Nanomed. 12 (2017) 3193–3206.
[111] S.K. Tripathy, Y.-T. Yu, Spectroscopic investigation of S–Ag interaction in ω-mercaptoundecanoic acid capped silver nanoparticles, Spectrochim. Acta. A Mol. Biomol. Spectrosc. 72 (2009) 841–844.
[112] X. Li, J. Zhang, W. Xu, et al., Mercaptoacetic acid-capped silver nanoparticles colloid: Formation, morphology, and SERS activity, Langmuir. 19 (2003) 4285–4290.
[113] G.C. Cotton, C. Gee, et al., Efficacy and safety of alpha lipoic acid-capped silver nanoparticles for oral applications, RSC Adv. 9 (2019) 6973–6985.
[114] A. Borowik, K. Butowska, et al., The impact of surface functionalization on the biophysical properties of silver nanoparticles, Nanomaterials. 9 (2019) 973.
[115] W. Wang, X. Chen, S. Efrima, Silver nanoparticles capped by long-chain unsaturated carboxylates, J. Phys. Chem. B. 103 (1999) 7238–7246.
[116] A. Chandra, M. Singh, Biosynthesis of amino acid functionalized silver nanoparticles for potential catalytic and oxygen sensing applications, Inorg. Chem. Front. 5 (2018) 233–257.
[117] G.H. Hermanson, Bio-conjugate Techniques, 2nd edition, Academic Press, San

Diego, Calif. USA, 2008.
[118] Z. Grabarek, J. Gergely, Zero-length crosslinking procedure with the use of active esters, Anal. Biochem. 185 (1990) 131–135.
[119] J.C. Sheehan, J. Preston, P.A. Cruickshank, A rapid synthesis of oligopeptide derivatives without isolation of intermediates, J. Am. Chem. Soc. 87 (1965) 2492–2493.
[120] M.J.E. Fischer, Amine coupling through EDC/NHS: A practical approach, in: N. Mol, M. Fischer (Eds.), Surface Plasmon Resonance. Methods in Molecular Biology (Methods and Protocols), vol 627, Humana Press, 2010.
[121] L.S. Jang, H.K. Keng, Modified fabrication process of protein chips using a short-chain self-assembled monolayer, Biomed. Microdevices. 10 (2008) 203–211.
[122] D. Bartczak, A.G. Kanaras, Preparation of peptide-functionalized gold nanoparticles using one pot EDC/SULFO-NHS coupling, Langmuir. 27 (2011) 10119–10123.
[123] S. Puertas, P. Batalla, M. Moros, E. Polo, P. del Pino, J.M. Guisán, et al., Taking advantage of unspecific interactions to produce highly active magnetic nanoparticle-antibody conjugates, ACS Nano. 5 (2011) 4521–4528.
[124] P. Prasher, M. Sharma, Tailored therapeutics based on 1,2,3-1H-triazoles: A mini review, MedChemComm. 10 (2019) 1302–1328.
[125] R. Manetsch, A. Krasinski, et al., In situ click chemistry: Enzyme inhibitors made to their own specifications, J. Am. Chem. Soc. 126 (2004) 12809–12818.
[126] Q. Shen, Y. Shan, Y. Lu, P. Xue, Y. Liu, X. Liu, Enhanced antibacterial activity of poly (dimethylsiloxane) membranes by incorporating SiO_2 microspheres generated silver nanoparticles, Nanomaterials 9 (2019) 705.
[127] N. Li, W.H. Binder, Click-chemistry for nanoparticle-modification, J. Mater. Chem. 21 (2011) 16717–16734.
[128] Y. Yao, D. Tian, H. Li, Cooperative binding of bifunctionalized and click-synthesized silver nanoparticles for colorimetric Co^{2+} sensing, ACS Appl. Mater. Interface. 2 (2010) 684–690.
[129] S.H. Lee, B.-H. Jun, Silver nanoparticles: Synthesis and application for nanomedicine, Int. J. Mol. Sci. 20 (2019) 865.
[130] A.L. Mohamed, A.G. Hassabo, S. Shaarawy, A. Hebeish, Benign development of cotton with antibacterial activity and metal sorpability through introduction amino triazole moieties and AgNPs in cotton structure pre-treated with periodate, Carbohyd. Polym. 178 (2017) 251–259.
[131] M.M. Chua, S.T. Fan, F. Karush, Attachment of immunoglobulin to liposomal membrane via protein carbohydrate, Biochim. Biophys. Acta. 800 (1984) 291–300.
[132] C.B. Hansen, G.Y. Kao, E.H. Moase, S. Zalipsky, T.M. Allen, Attachment of antibodies to sterically stabilized liposomes: evaluation, comparison and optimization of coupling procedures, Biochim. Biophys. Acta—Biomemb. 1239 (2) (1995) 133–144.
[133] S.M. Chamow, T.P. Kogan, D.H. Peers, R.C. Hastings, R.A. Byrn, A. Ashkenazi, Conjugation of soluble CD4 without loss of biological activity via a novel carbohydrate-directed cross-linking reagent, J. Biol. Chem. 267 (22) (1992) 15916–15922.
[134] E. Liu, M. Zhang, H. Cui, J. Gong, Y. Huang, J. Wang, Y. Cui, W. Dong, L. Sun, H. He, V.C. Yang, Tat-functionalized Ag-Fe_3O_4 nano-composites as tissue-penetrating vehicles for tumor magnetic targeting and drug delivery, Acta Pharm. Sin. B. 8 (2018) 956–968.
[135] F. Wang, B. Chen, B. Yan, Y. Yin, L. Hu, Y. Liang, M. Song, G. Jiang, Scattered light imaging enables real-time monitoring of label-free nanoparticles and fluorescent biomolecules in live cells, J. Am. Chem. Soc. 141 (2019) 14043–14047.
[136] C. Auria-Soro, T. Nesma, P. Juanes-Velasco, et al., Interactions of nanoparticles and biosystems: Microenvironment of nanoparticles and biomolecules in nanomedicine, Nanomaterials. 9 (2019) 1365.
[137] A. Roy, O. Bulut, S. Some, A.K. Mandal, M.D. Yilmaz, Green synthesis of silver nanoparticles: Biomolecule-nanoparticle organizations targeting antimicrobial activity, RSC Adv. 9 (2019) 2673–2702.
[138] V.S. Madamsetty, A. Mukherjee, S. Mukherjee, Recent trends of the bio-inspired nanoparticles in cancer theranostics, Front. Pharmacol. 10 (2019) Article 1264.
[139] S. Mohan, O.S. Oluwafemi, S.P. Songca, V.P. Jayachandran, D. Rouxel, O. Joubert, N. Kalarikkal, S. Thomas, Synthesis, antibacterial, cytotoxicity and sensing properties of starch-capped silver nanoparticles, J. Mol. Liquid. 213 (2016) 75–81.
[140] R. Augustine, A. Augustine, N. Kalarikkal, S. Thomas, Fabrication and characterization of biosilver nanoparticles loaded calcium pectinate nano-micro dual-porous antibacterial wound dressings, Prog. Biomater. 5 (2016) 223–235.
[141] S. Mohan, O.S. Oluwatobi, S.C. George, V.P. Jayachandran, F.B. Lewu, S.P. Songca, N. Kalarikkal, S. Thomas, Completely green synthesis of dextrose reduced silver nanoparticles, its antimicrobial and sensing properties, Carbohyd. Polym. 106 (2014) 469–474.
[142] P.D. Pietro, L. Zaccaro, D. Comegna, A.D. Getto, M. Saviano, R. Snyders, D. Cossement, C. Satriano, E. Rizzarelli, Silver nanoparticles functionalized with a fluorescent cyclic RGD peptide: A versatile integrin targeting platform for cells and bacteria, RSC Adv. 6 (2016) 112381–112392.
[143] M.A. Munoz-Morris, F. Heitz, G. Divita, M.C. Morris, The peptide carrier Pep-1 forms biologically efficient nanoparticle complexes, Biochem. Biophys. Res. Commun. 355 (2007) 877–882.
[144] V. Asgary, A. Shoari, F. Baghbani-Arani, S. Shandiz, M. Khosravy, A. Janani, et al., Green synthesis and evaluation of silver nanoparticles as adjuvant in rabies veterinary vaccine, Int. J. Nanomed. 11 (2016) 3597–3605.
[145] K. Banerjee, V.R. Rai, M. Umashanker, Effect of peptide-conjugated nanoparticles on cell lines, Prog. Biomater. 8 (2019) 11–21.
[146] D.G. Thompson, A. Enright, K. Faulds, W.E. Smith, D. Graham, Ultrasensitive DNA detection using oligonucleotide-silver nanoparticle conjugates, Anal. Chem. 80 (2008) 2805–2810.
[147] B.C. Vidal, T.C. Deivaraj, J. Yang, H.P. Too, G.M. Chow, L.M. Gane, J.Y. Lee, Stability and hybridization-driven aggregation of silver nanoparticle–oligonucleotide conjugates, New J. Chem. 29 (2005) 812–816.
[148] M.S. Cordray, M. Amdahl, R.R. Richards-Kortum, Gold nanoparticle aggregation for quantification of oligonucleotides: Optimization and increased dynamic range, Anal. Biochem. 431 (2012) 99–105.
[149] J.A. Dougan, C. Karlsson, W.E. Smith, D. Graham, Enhanced oligonucleotide-nanoparticle conjugate stability using thioctic acid modified oligonucleotides, Nucleic Acids Res. 35 (2007) 3668–3675.
[150] Z. Li, R. Jin, C.A. Mirkin, R.L. Letsinger, Multiple thiol-anchor capped DNA-gold nanoparticle conjugates, Nucleic Acids Res. 30 (2002) 1558–1562.
[151] aR Augustine, A. Hasan, V.K.Y. Nath, J. Thomas, A. Augustine, N. Kalarikkal, A.A. Moustafa, S. Thomas, Electrospun polyvinyl alcohol membranes incorporated with green synthesized silver nanoparticles for wound dressing applications, J. Mater. Sci. Mater. Med. 29 (2018) Article 163. b. M. Singh, P. Prasher, Ultrafine silver nanoparticles: Synthesis and biocidal studies, BioNanoScience. 8 (2018) 735-741.
[152] P. Jelinkova, A. Mazumdar, et al., Nanoparticle-drug conjugates treating bacterial infections, J. Control. Rel. 307 (2019) 166–185.
[153] L. Muthukrishnan, M. Chellappa, A. Nanda, S. Thukkaram, G. Selvaraj, B. Muthiah, S. Sagadevan, J.A. Lett, Bio-fabrication of pigment-capped silver nanoparticles encountering antibiotic-resistant strains and their cytotoxic effect towards human epidermoid larynx carcinoma (HEp-2) cells, RSC Adv. 9 (2019) 15874–15886.
[154] S. Mohanty, P. Jena, R. Mehta, R. Pati, B. Banerjee, S. Patil, A. Sonawane, Cationic antimicrobial peptides and biogenic silver nanoparticles kill mycobacteria without eliciting DNA damage and cytotoxicity in mouse macrophages, Antimicrob. Agents Chemother. 57 (2013) 3688–3698.
[155] E.M. Avila, G. Ferro-Flores, B.E. Ocampo-García, G. López-Téllez, J. López-Ortega, D.G. Rogel-Ayala, D. Sánchez-Padilla, Antibacterial efficacy of gold and silver nanoparticles functionalized with the ubiquicidin (29–41) antimicrobial peptide, J. Nanomater. 2017 (2017) Article ID 5831959.
[156] I. Pal, V.P. Brahmkhatri, S. Bera, D. Bhattacharyya, Y. Quirishi, A. Bhunia, H.S. Atreya, Enhanced stability and activity of an antimicrobial peptide in conjugation with silver nanoparticle, J. Colloid Interface Sci. 483 (2016) 385–393.
[157] V.P. Brahmkhatri, K. Chandra, A. Dubey, H.S. Atreya, An ultrastable conjugate of silver nanoparticles and protein formed through weak interactions, Nanoscale 7 (2015) 12921–12931.
[158] P.R. Lambadi, T.K. Sharma, P. Kumar, P. Vasnani, S.M. Thalluri, N. Bisht, R. Pathania, N.K. Navani, Facile biofunctionalization of silver nanoparticles for enhanced antibacterial properties, endotoxin removal, and biofilm control, Int. J. Nanomed 18 (2015) 2155–2171.
[159] A.A. Chaudhary, D. Ashmore, S. Nath, K. Kate, V. Dennis, S.R. Singh, D.R. Owen, C. Palazzo, R.D. Arnold, M.E. Miller, S.R. Pillai, A novel covalent approach to bioconjugate silver coated single walled carbon nanotubes with antimicrobial peptide, J. Nanobiotechnol. 14 (2016) Article Number 58.
[160] M. Bajaj, S.K. Pandey, N. Wangoo, R.K. Sharma, Peptide functionalized metallic nanoconstructs: Synthesis, structural characterization, and antimicrobial evaluation, ACS Biomater. Sci. Eng. 4 (2018) 739–747.
[161] B. Syed, M.N.N. Prasad, M. Kumar, S. Satish, Bioconjugated nano-bactericidal complex for potent activity against human and phytopathogens with concern of global drug resistant crisis, Sci. Total. Environ. 637–638 (2018) 274–281.
[162] E.Z. Gomaa, Synergistic antibacterial efficiency of bacteriocin and silver nanoparticles produced by probiotic *Lactobacillus paracasei* against multidrug resistant bacteria, Int. J. Peptide Res. Ther. 25 (2019) 1113–1125.
[163] S. Ramesh, M. Grijalwa, et al., Peptides conjugated to silver nanoparticles in biomedicine – A "value-added" phenomenon, Biomater. Sci. 4 (2016) 1713–1725.
[164] V. de Luca, A.M. Higa, C.M. Romano, G.P. Mambrini, L.A. Peroni, F.T. Strixino, F.L. Leite, Cross-reactivity between myelin oligodendrocyte glycoprotein and human endogenous retrovirus W protein: nanotechnological evidence for the potential trigger of multiple sclerosis, Micron 120 (2019) 66–73.
[165] A. Lizon, M.W. Sarna, M. Gajewska, R. Drozdz, Silver nanoparticle-based assay for the detection of immunoglobulin free light chains, Materials 12 (2019) 2981.
[166] N. Patra, et al., Antibacterial, anticancer, anti-diabetic and catalytic activity of bioconjugated metal nanoparticles, Adv. Nat. Sci: Nanosci. Nanotechnol. 9 (2018) 035001.
[167] H.L. Amand, H.A. Rydberg, L.H. Fornander, P. Lincoln, B. Norden, E.K. Esbjorner, Cell surface binding and uptake of arginine- and lysine-rich penetratin peptides in absence and presence of proteoglycans, Biochim. Biophys. Acta. 1818 (2012) 2669–2678.
[168] F. Heitz, M.C. Morris, G. Divita, Twenty years of cell-penetrating peptides: From molecular mechanisms to therapeutics, Br. J. Pharmacol. 157 (2009) 195–206.
[169] S.M. Farkhani, A.A. Fard, P. Zakeri-Milani, J.S. Mojarrad, H. Valizadeh, Enhancing antitumor activity of silver nanoparticles by modification with cell penetrating peptides, Artif. Cells Nanomed. Biotechnol. 45 (2017) 1029–1035.
[170] G. Ruan, A. Agrawal, A.L. Marcus, S. Nie, Imaging and tracking of tat peptide-conjugated quantum dots in living cells: new insights into nanoparticle uptake, intracellular transport, and vesicle shedding, J. Am. Chem. Soc. 129 (2007) 14759–14766.
[171] A. Mishra, V.D. Gordon, L. Yang, R. Coridan, G.C. Wong, HIV TAT forms pores in membranes by inducing saddle-splay curvature: Potential role of bidentate hydrogen bonding, Angew. Chem. Int. Ed. Engl. 47 (2008) 2986–2989.
[172] J. Liu, Y. Zhao, Q. Guo, Z. Wang, H. Wang, Y. Yang, Y. Huang, TAT-modified nanosilver for combating multidrug-resistant cancer, Biomaterials 33 (2012) 6155–6161.
[173] R.G.C. Pimentel, V.R. Botero, E.S.M. Martinez, Soybean agglutinin-conjugated

silver nanoparticles nanocarriers in the treatment of breast cancer cells, J. Biomater. Sci., Polym. Edn. 27 (2016) 218–234.
[174] S. Singh, D. Chitkara, R. Mehrazin, S.W. Behrman, R.W. Wake, R.I. Mahato, Chemoresistance in prostate cancer cells is regulated by miRNAs and Hedgehog pathway, PLoS ONE. 7 (2012) e40021.
[175] R. Fanciullino, J. Ciccolini, G. Milano, Challenges, expectations and limits for nanoparticles-based therapeutics in cancer: A focus on nano-albumin-bound drugs, Crit. Rev. Oncol. Hematol. 88 (2013) 504–513.
[176] A. Wicki, D. Witzigmann, V. Balasubramanian, J. Huwyler, Nanomedicine in cancer therapy: Challenges, opportunities, and clinical applications, J. Control. Release. 200 (2015) 138–157.
[177] S. Thomas, N. Kalarikkal, P.C.V.Z. Ahmad, J.T. Haponiuk, Functionalized engineering materials and their applications, CRC Press, Taylor & Francis Group, ISBN: 978-1-315-36554-1, Pages 402.
[178] N. Kalarikkal, S. Thomas, O. Koshy, Nanomaterials: Physical, chemical, and biological applications, CRC Press, Taylor & Francis Group, ISBN 9781771884617, Pages 408.
[179] S.M. Bhagyaraj, O.S. Oluwafemi, N. Kalarikkal, S. Thomas, Characterzation of nanomaterials, Advances and key technologies, Ist Edition, Woodhead Publishing, Elsevier, ISBN: 9780081019733, Pages 390.
[180] J. Krajczewski, K. Kolataj, A. Kudelski, Plasmonic nanoparticles in chemical analysis, RSC Adv. 7 (2017) 17559–17576.
[181] N. Kalarikkal, R. Augustine, O.S. Oluwafemi, K.S. Joshy, S. Thomas, Nanomedicine and tissue engineering: State of the art and recent trends, CRC Press, Taylor & Francis Group, ISBN 1498726429, Pages 562.
[182] K.B. Mogensen, K. Kneipp, Size-dependent shifts of plasmon resonance in silver nanoparticle films using controlled dissolution: Monitoring the onset of surface screening effects, J. Phys. Chem. C 118 (2014) 28075–28083.
[183] F.G. Ortega, M.A. Fernández-Baldo, M.J. Serrano, G.A. Messina, J.A. Lorente, J. Raba, Epithelial cancer biomarker EpCAM determination in peripheral blood samples using a microfluidic immunosensor based in silver nanoparticles as platform, Sens. Actuators B Chem. 221 (2015) 248–256.
[184] L.-J. Zhao, R.-J. Yu, W. Ma, H.-X. Han, H. Tian, R.-C. Qian, Y.-T. Long, Sensitive detection of protein biomarkers using silver nanoparticles enhanced immunofluorescence assay, Theranostics. 7 (2017) 876–883.
[185] A.M. Higa, G.P. Mambrini, J.C.M. Lerich, P.S. Garcia, J.A. Scramin, L.A. Peroni, N.M. Okuda-Shinagawa, M.M. Teres, F. Trivinho-Strixino, Peptide-conjugated silver nanoparticles for autoantibody recognition, J. Nanosci. Nanotechnol. 19 (2019) 7564–7573.
[186] J.-S. Lee, A.K.R. Lytton-Jean, S.J. Hurst, C.A. Mirkin, Silver nanoparticle-oligonucleotide conjugates based on DNA with triple cyclic disulfide moieties, Nano Lett. 7 (2007) 2112–2115.
[187] D.G. Thompson, A. Enright, K. Faulds, W.E. Smith, D. Graham, Ultrasensitive DNA detection using oligonucleotide-silver nanoparticle conjugates, Anal. Chem. 80 (2008) 2805–2810.
[188] Y. Liu, C.Z. Huang, One-step conjugation chemistry of DNA with highly scattered silver nanoparticles for sandwich detection of DNA, Analyst. 137 (2012) 3434–3436.
[189] S. Pal, J. Sharma, H. Yan, Y. Liu, Stable silver nanoparticle–DNA conjugates for directed self-assembly of core-satellite silver–gold nanoclusters, Chem. Commun. (2009) 6059–6061.
[190] I. Siddiqui, Q. Husain, Stabilization of polydopamine modified silver nanoparticles bound trypsin: Insights on protein hydrolysis, Colloid Surf. B. 173 (2019) 733–741.
[191] I. Lubitz, A. Kotlyar, Self-assembled G4-DNA-silver nanoparticle structures, Bioconjugate Chem. 22 (2011) 482–487.
[192] A. Abbaspour, F. Norouz-Sarvestani, A. Noori, N. Soltani, Aptamer-conjugated silver nanoparticles for electrochemical dual-aptamer-based sandwich detection of staphylococcus aureus, Biosens. Bioelectron. 68 (2015) 149–155.
[193] H. Li, H. Hu, et al., Multifunctional aptamer-silver conjugates as theragnostic agents for specific cancer cell therapy and fluorescence-enhanced cell imaging, Anal. Chem. 87 (2015) 3736–3745.
[194] Q. Tang, N. Wang, F. Zhou, S. Zhang, et al., AgNPs/DNA/TPdye conjugate-based two-photon nanoprobe for GSH imaging in cell apoptosis of cancer tissue, Chem. Commun. 51 (2015) 16810–16812.
[195] H. Sun, J. Kong, Q. Wang, Q. Liu, X. Zhang, Dual signal amplification by eATRP and DNA-templated silver nanoparticles for ultrasensitive electrochemical detection of nucleic acids, ACS Appl. Mater. Interfaces. (2019), https://doi.org/10.1021/acsami.9b08037.
[196] V. Nasirian, A. Chabok, A. Barati, M. Rafienia, M.S. Arabi, M. Shamsipur, Ultrasensitive aflatoxin B1 assay based on FRET from aptamer labelled fluorescent polymer dots to silver nanoparticles labeled with complementary DNA, Microchim. Acta 184 (2017) 4655–4662.
[197] A.D. Kurdekar, L.A.A. Chunduri, S.M. Chelli, et al., Fluorescent silver nanoparticle based highly sensitive immunoassay for early detection of HIV infection, RSC Adv. 7 (2017) 19863–19877.
[198] Y. Khristunova, E. Korotkova, Preparation and investigation of silver nanoparticle–antibody bioconjugates for electrochemical immunoassay of tick-borne encephalitis, Sensors. 19 (2019) Article 2103.
[199] S. B-Farcau, M. Potara, T. Simon, A. Juhem, P. Baldeck, S. Astilean, Folic acid-conjugated, SERS-labeled silver nanotriangles for multimodal detection and targeted photothermal treatment on human ovarian cancer cells, Mol. Pharm. 11 (2014) 391–399.
[200] C.-W. Yen, H. de Puig, J. Tam, et al., Multicolored silver nanoparticles for multiplexed disease diagnostics: Distinguishing dengue, yellow fever, and ebola viruses, Lab Chip. 15 (2015) 1638–1641.
[201] R. Mehra, V. Chiang, K. Aron, J. Frisz, Signal amplification in solution-based plasmonic specific-binding partner assays, (2019) US10429383B2.
[202] A kind of gold, silver nanoparticle chiral dimer of detectable 8-OHdG, (2019) CN109187446A.
[203] Specific recognition and detection method for ribonucleic acid using boronic acid modified nanoparticle system, (2019) WO2019153137A1.
[204] C.A. Mirkin, D.A. Giljohann, D. Seferos, A.E. Prigodich, P.C. Patel, Polyvalent RNA-nanoparticle compositions, (2018) EP3335705A1.
[205] S. Mohapatra, S. Mohapatra, Nanoparticle-enhanced enzymatic immune biosensor assay for antigen detection, (2018) WO2018200829A1.
[206] One kind is based on DNA-silver nanoclusters structure Electrochemiluminescsensor sensor, preparation and its application, (2018) CN108663354A.
[207] Biosensor detecting mercury ion using conjugates of virus and silver nanoparticle, (2019) KR20190110247A.
[208] T. Ruzgas, et al., Improved biosensor and method for manufacturing such, (2019) WO2019139537A1.
[209] Method for measuring fibrinogen concentration in blood sample, and nanoparticles therefore, (2019) WO2019203486A1.
[210] Y.W.C. Cao, Devices for detecting target biological molecules from cells and viruses, (2019) US20190323069A1.
[211] Method for detecting mutation of gene using aggregation of gold nanoparticle, (2019) WO2019022385A1.
[212] Sensor for detection of gene mutation using resonance frequency shift, (2019) KR101991593B1.
[213] Multiplexed immunoassay for detecting biomarkers of disease, (2018) WO2018237227A1.
[214] C.M. Klapperich, G.W. Pratt IV, A. Fan, Tenofovir detection assay, (2018) US20190025334A1.
[215] J.C. Jones, A.M. Kastresana, J.A. Berzofsky, J. Welsh, A. Rosner, US20190242887A1, (2019).
[216] A kind of preparation method of the composite nanoparticle probe of how mercapto-modified covalent coupling antibody, (2018) CN108226477A.