Chapter

Metal-Based Nanomaterials Photodynamic Action with a Focus on Au and Ag Nanomaterials

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Abstract

Photodynamic action is the interaction between cells and oxygen, light, and chemical reagent (photosensitizers). Photodynamic techniques include photodynamic diagnosis (PDD), fluorescence-guided tumor resection, and photodynamic therapy (PDT). PDD and PDT have the exact mechanism. They are based on light and tissue interaction with a difference. PDT is along with the destruction of the lesion against PDD that the diagnosis is made without destruction. Photosensitizers (PSs) could be organic and inorganic. Metal-based PSs were considered, due to the disadvantages of organic PSs such as low quantum yield and small stock shift, and high toxicity. We have examined the metal-based nanomaterials PDT in recent years. The titles considered are including the introduction that consists of explanations about photodynamic action, PDD, PDT and history of PDT, PDT mechanism, PDT effects on the immune system, photosensitizers, and metal-based nanomaterials in the photodynamic application, which this section addresses along with the application of metal nanomaterials (with a focus on gold and silver nanomaterials) in photodynamic techniques.

Keywords: photodynamic, metal nanomaterials, photosensitizers, gold nanoparticles, silver nanoparticles

1. Introduction

Photodynamic is defined as the effect of light on living systems in combination with oxygen and chemical reagents. Photodynamic diagnosis (PDD), fluorescence-guided tumor surgery (FGS), and photodynamic therapy (PDT) are most recent types of photodynamic technology. FGS is the use of fluorescence imaging in surgery for defining tumor location and its margins. PDT and PDD are non- or minimally invasive therapeutic and diagnosis techniques. PDD is an effective diagnosis method with a wide application in medical diagnosis including dermatology, gastroenterology, urology, and oncology. Similar to PDT, the mechanism of PDD is based on light and tissue interaction but does not along with the destruction of the lesion. When a specific wavelength of light is irradiated to a tissue, endogenous or exogenous

fluorophores absorb the light energy leading to electrons being raised to an excited state, and subsequent relaxation and returning to the ground state lead to emission fluorescence of a specific wavelength [1–7].

Photodynamic therapy (PDT) is a form of phototherapy and the joint action of nontoxic photosensitizer (PS), a light source, and molecular form of oxygen. The PS, in the presence of oxygen, is activated by a suitable wavelength of light to generate reactive oxygen species (ROS) (**Figure 1**). This phototoxicity leads to oxidative stress and cytotoxicity to elicit cell injury and cell death [5, 8–10]. PDT has been used clinically to treat a wide range of neoplastic and non-malignant diseases with minimal side effects on the surrounding normal cells. PDT was approved by the US Food and Drug Administration as the first drug-device combination for cancer therapy [3, 11]. In addition to oncological diseases, PDT is a very efficient therapeutic modality for non-oncological diseases. Recently, PTD was used as a new approach for elimination of human pathogens too. Microbial infections continue to be an outstanding cause of morbidity and mortality worldwide. The wide utilization of antibiotics and vaccination strategies cannot avert the prevalence of microbial infections. Frequent and immeasurable utilization of antimicrobial drugs may be associated with side effects such as gastrointestinal disorders, liver toxicity, and secondary fungal infections. These factors sternly diminish the therapeutic effect of antimicrobials and develop drug resistance in microbes. By broad monitoring commissioned by the UK Government and Wellcome Trust in 2016, it has been estimated that mortality of antimicrobial resistance will rise to over 10 million worldwide by 2050. Some clinical trial studies have demonstrated that microbial infection could be diminished using PDT techniques. To this, PS as a photodynamic agent suitably is engineered to target the structural elements of microbial cells selectively. Despite PDT advantages, there are some limitations such as effective PS with properties of an ideal PS, leading to reduce the efficacy of PDT. Nanotechnology-based PDT and combination therapy including chemotherapy, radiotherapy (RT), immunotherapy and anti-angiogenesis therapy, hypothermia, and employment of antioxidants and receptor inhibition strategies

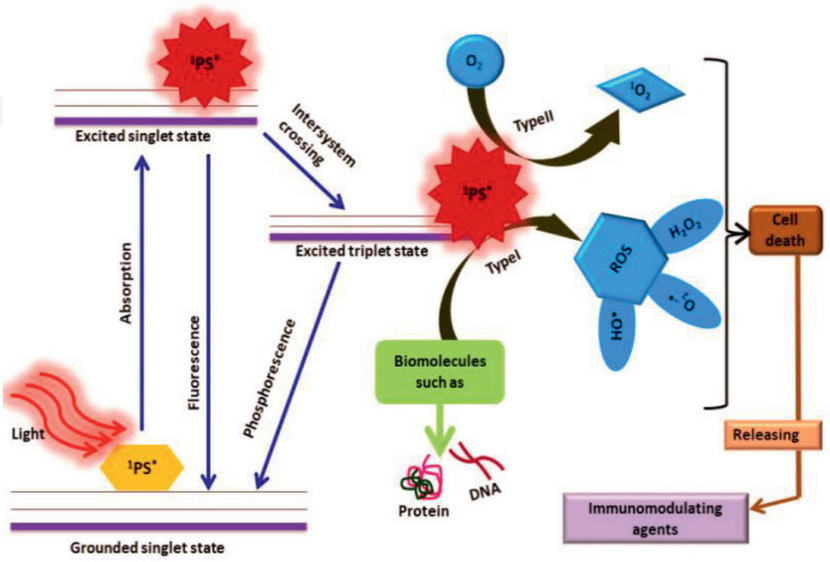

Figure 1.
Schematic illustration of PDT mechanism. PS reaches to $^1PS^*$ through absorption of light with specific wavelength. The $^1PS^*$ undergoes intersystem crossing to an $^3PS^*$ (an electronically different excited state lower in energy). $^3PS^*$ generates ROS through interaction with the surrounding biomolecules.

during PDT are methods to overcome these obstacles. Nanotechnology has garnered a great deal of attention in PDT, due to targeting potential and selective accumulation at the desired site and reduced toxicity to normal cells and tissues, improving the solubility of hydrophobic PSs and controlling the released rate of PSs. Nanoparticles have been used as PSs, conjugating agents, and carriers for PSs, followed by the creation of the fourth generation of PSs [8, 12–15]. This review article addresses the metal nanomaterial-based photodynamic applications in recent years. The main focus of this paper is on the application of silver and gold nanomaterial-based photodynamic therapy in recent years.

2. Photosensitizers

PSs are agents that absorb light of a specific wavelength, triggering the activation processes leading to the selective demolition of the improper cells [9]. Several PSs have already received FDA approval for use in photodynamic treatment for various types of cancer [2]. The physicochemical and biological characteristics of a PS could be summarized as the following: (1) composition uniformity, purity, and negligible of dark toxicity; (2) high clearance from the body patients [12]; (3) excellent solubility in body tissues; (4) stability at room temperature [9]; (5) potent absorption with a high extinction coefficient at near-infrared (NIR) wavelength range (700–1300 nm), where tissue penetration is increased, and the auto-absorption is reduced by other endogenous molecules (such as the hemoglobin); (6) inexpensive, affordable, and easy to synthesize; (7) the capability of high tumor selectivity and subcellular targeting [16].

There are different categorizations for PSs. PSs can be categorized based on their response to NIR light: direct NIR-responsive PSs and indirect NIR-responsive PSs. The direct PSs can directly convert light energy into the production of radical agents, and they are composed of NIR-responsive organic and inorganic PSs. The indirect PSs include UV- or visible light responsive PSs and an up-conversion nanomaterial.

Based on the time of application, PSs are classified into four distinct generation categories. The first generations are based on hematoporphyrin and its derivatives (e.g., Photofrin, Photosan, and Photocan), acridine dyes, and eosin solution. Photofrin (the trade name of sodium porfimer) is a mixture of purified porphyrin dimers and oligomers from hematoporphyrin derivatives. The limitations of the first-generation PSs include low penetration into tissues due to short wavelength of maximum absorption, low chemical purity, long half-life, and high accumulation in the skin that lead to skin hypersensitivity to light leading to investigate the next generation of PSs. The second generation of PSs, which have better chemical purity, consist of hematoporphyrin derivatives, synthetic PSs such as 5-aminolevulinic acid, and pure synthetic compounds of an aromatic macrocycle such as porphyrins, benzoporphyrins, and chlorins. Moreover, PSs of this generation show higher quantum yield of $^1O_2$ production, better tissue penetration due to maximum absorption in the wavelength of 650–800 nm, improved selectivity for target tissue, and fewer side effects, extended extinction coefficient. Despite such mentioned benefits of second-generation PSs, they have poor solubility in water, which limits their intravenous administration.

Third-generation PSs are developed by altering existing PSs from earlier generations and combining them with nanomaterials or substances that have a higher affinity for tumor tissue. These modifications can include combination with target

receptor ligand molecules and LDL lipoprotein, conjugation with a monoclonal antibody specific for cancer cell antigen, and the use of tumor surface markers. Increased selectivity, greater accumulation in the target site, better bioavailability, and reduced therapeutic doses to produce satisfactory therapeutic effects are among the benefits of third-generation photosensitizers [9, 11, 17].

Next generation of PSs are nanomaterial-based PSs and living-organism-derived, protein in the name of genetically encoded photosensitizers (GEPSs) has been developed. GEPSs are more beneficial than synthetic PSs due to their facility intracellular localization, spatiotemporal protein expression, and ROS generation through designing with genetic engineering methods as following selective and controlled expression by using particular promotors, efficient PSs owning to high speeding of intersystem crossing and excited triplet state generation, the study of the mechanisms that occur in living cells by recruitment chromophore-assisted light inactivation (CALI), PDT, correlative light-electron microscopy (CLEM) and photoablation, widely high-specific targeting capability, reducing toxicity by proteolysis and spatiotemporal inactivation of cellular proteins. Due to the mentioned features, GEPS is an effective tool in biomedical applications such as PDT, immune PDT, antimicrobial PDT

FPPS	Features	Source	Ref.
KillerRed	Red fluorescent protein and the first GEPS, ROS generation through the type-I mechanism of PDT	Arised from non-fluorescent hydrozoan jellyfish-derived chromoprotein	[18]
KillerOrange	A dimeric orange variant, mechanism of ROS generation is similar to KillerRed	Developed from KillerRed	[18]
SuperNova Red (SNR)	Monomeric variant, expression of SNR in the cell as a fusion partner with various cellular proteins	Developed from KillerRed	[18]
SuperNova Green(SNG)	A monomeric variant and a green emitting PS protein	Developed from KillerRed	[18]

Table 1.
Fluorescent protein photosensitizers.

FBPS	Features	Source	Ref.
Mini singlet oxygen generator (MiniSOG)	A green-emitting and monomeric PS protein, surrounded by binding positions to flavin mononucleotide(FMN) chromophore as a required cofactor for ROS generation	Generated from an *Arabidopsis thaliana*-derived light-oxygen-voltage-sensing (LOV) domain of phototropin-2	[18]
Singlet oxygen protein PSs (SOPP)	Generated from site-directed mutagenesis, mutation of FMN-binding glutamine in SOPP to leucine (Q102L), improved photosensitizing performance	Developed from of MiniSOG	[18]
Pp2FbFP	A monomeric flavin binding PS with variants such as Pp2FbFP Y112L, Pp2FbFP Q116V, and Pp2FbFP L30M	Arised from *Pseudomonas putida*	[18]

Table 2.
Flavin-binding photosensitizers.

(aPDT), and CALI. Oligomeric and monomeric types of GEPS have been utilized in cellular applications with photophysical features. GEPS-based photosensitizers could be categorized into fluorescent protein photosensitizers (FPPSs) (**Table 1**) and flavin-binding photosensitizers (FBPSs) (**Table 2**) [18].

2.1 PDT mechanism

After light irradiation, PS absorbs a quantum of light and will reach its excited singlet state ($^1PS^*$). The single excited PS undergoes intersystem crossing to an excited triplet state ($^3PS^*$). During this transfer, part of the energy is irradiated in the form of a quantum of fluorescence.$^3PS^*$ produces ROS through interaction with the surrounding biomolecules via type I and type II mechanisms. In the type I reaction, excited triplet state $^3PS^*$ reacts directly with biomolecules such as cell membrane, then transferring hydrogen or electron between PS and substrate, leading to the formation of highly reactive products of the PS and the substrate including hydroxyl radicals ($HO^\bullet$), superoxide anion ($O_2^{-\bullet}$), and hydrogen peroxide (H_2O_2). After the start of the radical chain reactions, cell components will begin to be destroyed, which will cause the signaling pathways for autophagy or apoptosis to be triggered. In the type II mechanism, $^3PS^*$ transfers directly energy to the molecular oxygen in the ground triplet state to form excited singlet oxygen ($^1O_2$) having high quantum yields. On the other hands, $^1O_2$ produced by type II reaction increases the level of ROS that causes damages to proteins, nucleic acids, lipids, membranes, and organelles, which can lead to activation of cell death processes such as apoptosis or necrosis [9, 10, 15].

3. Metal-based nanomaterials in photodynamic application

Nanomaterials usually refer to materials that possess at least one dimension in sizes ranging from 1 to 100 nm. They can be used alone as a PS or conjugated with PS and GEPS, in various types of PDT such as antimicrobial PDT and immune-PDT. Lipid PS nanoparticles (LPNs), polymer PS nanoparticles (PPNs), inorganic PS nanoparticles (IPNs), and self-assembled PS nanoparticles (SAPNs) are four groups of nanoparticles-based PSs in which IPNs are addressed in this review [18].

Due to the limitations of organic PSs, which include small stoke shift in porphyrin derivatives and low quantum yield due to aggregated form of porphyrin derivatives by steady p–p stacking in concentrated solutions, high toxicity, non-selectivity for tumor, and poor light absorption such as suboptimal tumor selectivity and poor light penetration into the tumor in second-generation PS, the interest of metal-based nanomaterial for PDT has been growing. Metal-based nanomaterials have been utilized as PSs and delivery vehicles because of properties that include: (1) relatively narrow size of metal nanoparticles, which can affect circulation time in the bloodstream and accumulation rate in tumors. Longer circulation time could be observed in therapeutic nanoparticles with a size of lower than 100 nm and higher accumulation in therapeutic nanoparticles with 20–200 nm size. (2) Shape distribution of metal nanoparticles that play a critical role in their internalization into the targeted cell. (3) Metal nanoparticles show surface plasmon resonance (SPR), which is associated with the surface plasmon resonance of the nanoparticles with a size smaller than the resonant absorption wavelength, used in PTT. According to this, the light wavelength used in PDT should be longer than the wavelength range of surface plasmon resonance. (4) Stability in water dispersion and long-term activity [11, 12, 19]. (5) Lower

PS leaching and higher loading efficiency of PSs. (6) High ability to interact with many compounds and generate both active and passive PS adsorption via the EPR effect [20]. Integration of PSs to nanoparticles is done via electrostatic or covalent interactions [21]. Subsequently, we discuss about various metal-based nanomaterials such as copper, O_2 self-enriched metal-based nanoplatforms, transition metal oxides (TMOs), and transition metal dichalcogenides (TMD), upconversion (UCNPs) and metal organic frameworks. After that, we concentrate on photodynamic therapy based on gold and silver nanomaterials.

Copper ions have a vital role in biosystems including proliferation and differentiation of cells, promoting angiogenesis by stabilizing the expression of hypoxia-inducible factor (HIF-1α) and secretion of vascular endothelial growth factor (VEGF), cell migration, accelerating wound healing by collagen deposition, keeping the immune system functioning in such a way that copper ion deficiency causes immunodeficiency through reducing the phagocytic activity of granulocytes and the immunoglobulins synthesis, copper-composed nanomaterials have biomedical applications including antibacterial applications such as anti-multidrug-resistant bacteria and Cu-based enzymes, drug delivery, bioimaging, bioeffect and biosafety, catalytic nanotherapeutics, and nanotherapy. Due to photonic properties, Cu-based nanomaterials are used in PTT and PDT [12, 22]. In 2020, tumor microenvironment (TME) stimuli-responsive theranostic nanoplatform via assembling PS (chlorine e6, Ce6) modified carbon-dots (CDs-Ce6) and Cu_2^+ is designed. The existence Cu_2^+ in this nanoplatform creates extra chemodynamic therapy (CDT) via $^{\bullet}OH$ generation through reaction with endogenous H_2O_2. Also, it enhances therapeutic efficiency by supernormal intracellular glutathione (GSH) depletion via a redox reaction This nanoplatform shows important features of FL imaging, synergistic treatment by PTT, PDT, and CDT [23].

Metal–organic frameworks (MOFs) are a kind of coordination polymers, which are usually composed of a metal oxide center and organic linkers. MOFs formed by self-assembly of metal ions clusters and organic ligands through the coordination bonds. MOFs have shown characteristics such as tunable sizes/shapes, high porosity, versatility, intrinsic biodegradability, well-defined biocompatibility, designable and ease of synthesis, and great drug delivery. They are multifunctional composites that enhance the PDT effect with other therapeutic modalities synergistically. PS molecules incorporate in MOF pores, therefore self-quenching and aggregation of PS molecules don't occur, and the distribution of ROS throughout the porous and rigid structure of MOF is easily accomplished [12, 24–27]. Nanoscale metal–organic frameworks (nMOFs) have potential characteristics, which lead to great biomedical applications. These properties include synthetic tunability in structures and compositions of nMOFs, high molecular payloads without self-quenching in photosensitizers, and facilitated diffusion of ROS through nMOFs pores to enhance the efficacy of PDT, radiotherapy (RT), radiotherapy-radiodynamic therapy (RT-RDT), and CDT, also reduce the adverse effect of hypoxia in aggressive tumors, which is based on evidence, hypoxia-inducible factor 1 (HIF-1) pathway activation triggers survival signaling in cancer cells. nMOFs could be used as immunoadjuvants, which leads to adaptive immunity boosting and PDT efficiency improvement. Passive and active targeting, regulation of singlet oxygen generation, innate biodegradability, prohibition of ROS neutralization, the capability of theranostic function, pH-responsive treatment of cancer [13, 26, 28, 29].

Transition metal oxides (TMOs) exhibit semiconductors such as properties including adjustable and different bandgaps, conductivity, absorption of light at

certain wavelengths, various proportions of oxygen's and metals, consequently creating various structures, photocatalytic efficiency, and possible wide usage of them in the PDT/PTT fields. The process of photo-catalysis is as follows: photons with energy equal to or greater than the TMO bandgap energy cause the excitation of electrons from the valence band to the conduction band (CB) and create electronic holes. These electrons and created holes during redox reactions, and adsorption of molecules to the surface of TMOs causes the creation of free radicals such as hydrogen peroxide (H_2O_2), superoxide ion ($O_2^{\bullet-}$), and hydroxyl radicals ($OH^{\bullet}$). ZnO, TiO_2, MoO_3, and WO_3 are among the TMOs that have great photo-induced antibacterial activity. Doping metal ions in TMOs, which maintains charge balance due to the presence of oxygen vacancies, is one method for increasing photocatalytic activity. TMOs have improved photocatalytic efficiency. There can be polymorphism due to the possibility of their synthesis manipulation that nanofibers, nanorods, nanobelts, and nanowires are instances of their diverse forms [2]. For example, the tubular structure of TiO_2 can perform as photocatalysis-propelled micro/nanomotors, and in an environment containing H_2O_2 (1%), O_2 bubbles are produced due to the decomposition of H_2O_2. Titanium dioxide (TiO_2), iron oxide, and cerium oxide are among the TMOs that can induce the lysosome-autophagy system through different pathways. TiO_2 is one of the common TMOs that has attracted a lot of attention in biomedicine due to its low cost, chemical stability, and biocompatibility, including as PSs in PDT, anticancer, and surface coating, and substrates for stem cell expansion. TiO_2 is usually an n-type semiconductor that has four polymorphisms. Anatase and rutile forms have efficient photocatalytic applications due to their broader band gap [14].

Transition metal dichalcogenides (TMDs) are semiconductors with stacking configurations and several structural phases. TMDs' structural phases are the coordination of the three atomic planes of transition metal (group IV, V, VI, VII, IX, or X) and two chalcogenides (S, Se, and Te). TMDs have bandgap energies within the range of 1.6–2.4 eV, which are suitable for visible light catalysis. TMDs act as co-catalysts and link to other photocatalysts. TMDs have electron sinks so they could retard photogenerated electron–hole recombination, which causes it widely used in photodynamic therapy and biosensing. Molybdenum disulfide (MoS_2) is one of the TMDs with poor cytotoxicity and higher NIR absorption. MoS_2 as a member of graphene-analog materials has graphene-derived features such as superior surface-to-volume ratios and hydrophobic surface nature leading to absorbing biomolecules, hydrophobic drugs, and genes, so it could be a drug delivery vehicle. According to studies, MoS_2 has PDT ability without adding other PSs. For example, MoS_2 nanoflowers have high NIR absorption and peroxidase-like activity, leading to decomposition of a low concentration of H_2O_2 and hydroxyl radical generation. Also, MoS_2 QDs could generate $^1O_2$ with radiation of 630 nm laser light [2, 30].

Upconversion NPs (UCNPs) and quantum dots are two major groups of transducing nanoparticles. The limited penetration depth of UV and visible light is a challenge for PDT, so transducing nanoparticles are a solution for this challenge so that they could transfer energy with wavelength out of PSs' absorption range to conjugated PS molecules Quantum dots (QDs) as semiconductor nanocrystals are constructed of different elements such as silicon, cadmium, selenide, and graphene, and they have optical and emission properties – dependent size (1–10 nm). QDs with larger sizes after that are excited by a specific wavelength of light, emitting light with low energy in the red spectrum range while the emission wavelength of smaller QDs is in the blue spectrum range. QDs could generate ROS by transferring energy to triplet oxygen, but their $^1O_2$ yield is low so it is necessary to design QDs conjugated with PSs

that have enhanced energy transfer for increasing $^1O_2$ yield [2, 15]. Other groups of nano-transducer are UCNPs, constructed of a crystalline host lattice that may possess transition metals, lanthanide, or actinide ions, such as ytterbium (Yb^{3+}), erbium (Er^{3+}), and thulium (Tm^{3+}) [15, 31].UCNPs provide anti-stoke luminescent because they could generate short-wavelength light (visible or UV light) from short-wavelength incident light (NIR). Up-conversion luminescence (UCL) efficiency depends on dopant ion ratio and up-conversion luminescence mechanisms.

Excited state absorption (ESA), photon avalanche (PA), and energy transfer up-conversion (ETU) are three main mechanisms that are observed in UCNPs either alone or in combination, for a luminescent generation. Energy transfer is the dominant mechanism that is existence in UCNPs such as $NaYF_4$ doped with Yb^{3+} (sensitizer), Er^{3+}, or Tm^{3+} (activator). ETU mechanism occurs in a two-ion-involved system, in which one of them donates energy is named sensitizer (S) ion and the other is activator (A) with the ability of visible or UV light emission. Each of the two neighboring ions absorbs the same energy, when the excited state of S and A is near enough, non-radiative energy transferring occurs from S to A, then the activator is excited to the upper energy state and emits higher-energy photons, while sensitizer comes back to ground state [2, 31, 32]. UCNPs could act as PSs, drug delivery systems, and bioconjugated, so they have wide applications in PDT including deep tumors PDT, antimicrobial PDT, and the PDT of viral infections. UCNPs such as lanthanides-doped platforms could incorporate into the design of MOF-based hybrid nanomaterials and act as a wavelength-shifting platform to broaden the light-harvesting properties of MOFs, which could absorb NIR light [2, 31, 33].

3.1 O_2 self-enriched metal-based nanoplatform for PDT improving

Due to requiring a high concentration of O_2 for PDT, one of the obstacles in PDT of solid tumors is the lack of enough oxygen because of the hypoxic microenvironment existence. The hypoxic microenvironment is a marking of solid tumors (50~60% of malignant solid tumors are recognized by hypoxia), which creates through imbalance between the oxygen consumption caused by tumor cell reproduction and insufficient oxygen supply created by tumor vascular systems abnormally. In addition to creating tumor resistance to PDT, hypoxia causes tumorigenesis and tumor progression, which can result from the production of hypoxia-inducible factors (HIFs), DNA methylation, and also the production of unwanted metabolites such as hydrogen peroxide (H_2O_2), which promotes tumor cell metastasis and invasion. Strategies for hypoxia relieving and PDT efficacy improvement, including: (1) hyperbaric oxygen therapy; (2) direct transport to tumor sites by oxygen-carrying agents (e.g., hemoglobin and perfluorocarbon); (3) in situ production of oxygen by degradation of chemicals (such as C_3N_4 and CaO_2), which is delivered by nanomaterials into tumor sites; (4) O_2 generation by catalytic conversion of some common appearances of ROSs such as $O_2^{\bullet-}$ and H_2O_2 into the tumor microenvironment. Pathophysiologic mechanisms (e.g., NADPH oxidase (NOX) enzymes overexpression), in tumors, lead to the production of elevated H_2O_2 that has a generation rate of 5 nmol per 105 cells h^{-1}.

Catalysis of endogenous H_2O_2 and conversion to O_2 are carried out by natural catalase and catalyze-like oxygen generators or artificial enzymes such as manganese dioxide (MnO_2), copper oxide (CuO), nanozymes, and biocatalytic cascades. Due to high sensitivity to TME and fast decomposition in an acidic environment, MnO_2 nanostructures were considered a TME-responsive drug carrier. MnO_2 and its various forms (e.g., MnO_2 nanosheets, MnO_2 nanoshell, and MnO_2 nanozymes) enhance

PDT efficacy through interaction with tumoral H_2O_2, as a result, O_2 generation and ameliorating tumor hypoxia. Also, MnO_2 moderates intratumoral GSH, as follows after MnO_2 interaction with GSH, Mn^{4+} converts to $Mn^{2+,}$ which can form hydroxyl radical($^{\bullet}OH$), through Mn^{2+} interaction with H_2O_2 by Fenton-like catalytic reaction. Tumor overexpressed GSH as a scavenger of ROS, causing tumor cells to become resistant to PDT-induced oxidative stress, thus reducing the efficiency of photodynamic therapy with intratumoral GSH. Nanozymes have enzyme mimetic activity. Nobel metal nanomaterials (such as platinum (Pt), palladium (Pd) nanoparticles, rhodium (Rh)-based nanomaterials), and cerium oxide nanoparticles have served as nanozymes and generate oxygen to promote ROS production for PDT of tumor cells. Rh decomposes H_2O_2 into O_2 through its catalase-like activity, and Rh alloys have a more catalytic effect. Cerium oxide (ceria, CeO_2) nanoparticles have the dual performance of superoxide dismutase (SOD) and catalase-like activity and could generate oxygen via the $O_2^{\bullet-}$and H_2O_2 catalysis. The bifunctional activity of ceria is the result of electron shuttle between Ce^{3+} and Ce^{4+}, which are mixed valence states, as follows Ce^{3+} decompose superoxide anion ($O_2^{\bullet-}$) and Ce^{4+} catalysis hydrogen peroxide (H_2O_2). Natural catalase's poor stability and nonporous properties of artificial enzymes reduce $^1O_2$ yield and their effect on the tumor environment hypoxia. Also, the amount of H_2O_2 produced by tumor cells is not large enough that artificial enzymes have a good catalytic function and generate a high amount of O_2. For this reason, smart biocatalytic cascade systems designed such as well-assembled multicatalytic nanoreactors have been interested. These systems can supply a large amount of molecular oxygen as a substrate for PDT and also provide more effective communication between catalyst and substrate in these systems [27, 34–36].

3.2 Gold-based nanomaterials

Gold nanomaterials (AuNMs) have different biomedical applications such as PTT and PDT, due to their physicochemical properties, **Figure 2**.

AuNMs features are including ease and the possibility of achieving different sizes of synthesis, flexibility in surface modification, great nanocarriers for transporting a wide range of components such as small molecules, nucleic acids, proteins, and antibodies, controlled-release, site-specific triggering, low toxicity, high conductivity, and localized surface plasmon resonance (LSPR). LSPR is one of the optical properties of AuNMs, which refers to the total oscillations of the conduction band electrons of metal nanoparticles. The absorption band of LSPR in AuNMs is affected by shape and aspect ratio, so that with tuning the shape and aspect ratio due to the surface photon confinement effect, the absorption spectrum reaches to NIR range. AuNMs are one of the NIR-responsive materials that have an absorption spectrum with a longer wavelength in the range of NIR (750–1000 nm), where the depth of light penetration into the target tissue is greater in this range. Therefore, they overcome the organic PSs' limitations, whose absorption spectrum has a shorter wavelength (300–700 nm) and a lower penetration depth (less than 1 mm) and can create a novel generation of PSs [2, 3, 37–40]. Gold nanoparticles' (Au NPs) appropriate wavelength for PDT is between 800 and 900 nm [12].

Au NPs can exist in different shapes, such as spheres, rods, shells, stars, cages, and gold nanoflowers, **Figure 2**. Au NPs can be isotropic and anisotropic based on their shapes and characteristics. Just as the size alterations affect the plasmon absorption band, the geometry alterations of the nanoparticles also affect the SPR band, so according to Mie's theory, the particle's electric surface charge density changes with

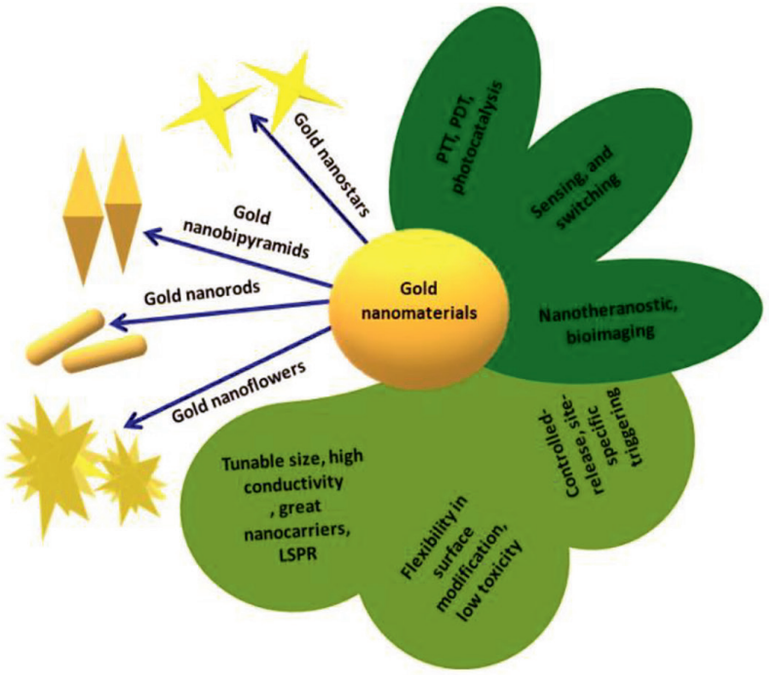

Figure 2.
Au NMs: shapes, features, and applications.

the alteration of the particle diameter. Therefore, with the increase in size, a shift in the location of the SPR absorption band toward longer wavelengths is observed. In addition, a small change in the particle geometry causes significant changes in the characteristics of the SPR absorption band. These alterations are also observed in anisotropic AuNPs, which are even higher than the changes caused by the increase in size in isotropic AuNPs. Anisotropic AuNPs have multiple SPR absorption bands contrary to the isotropic morphology, which has only one SPR absorption band. Therefore, the wavelength of the SPR absorption band shifts from the visible region to the near-infrared region (NIR), by changing the shape of the gold nanoparticle. Among the anisotropic morphologies of AuNPs, we can mention gold nanoflowers (AuNFs), gold nanostars (GNSs), gold nanorods (AuNRs), gold nanoplates, etc. Due to their anisotropic shape and symmetric structure with branches, GNSs possess tunable localized surface plasmon resonance (LSPR) in the near-infrared (NIR) region of the electromagnetic spectrum, and they are appropriate nanoplatforms for theranostic applications [3, 37, 41, 42].

The GNS@ICG-Ab-CIK nanoplatform designed by Shujing Liang et al. in 2020 is a nano-theranostics system that has the potential for cancer theranostics. In this nanoplatform, GNS (gold nanostars) was combined with anti-HER2 (trastuzumab) and targeted. Anti-HER2 (trastuzumab) is a monoclonal antibody that acts against HER2-overexpressing human breast cancer cells. This monoclonal antibody prevents cell cycle progression and inhibits angiogenesis and antibody-dependent cytotoxicity. GNS combined with trastuzumab was loaded with Indocyanine green (ICG) through electrostatic adsorption, and a new nanoprobe was formed that has the ability of tri-model imaging (photoacoustic (PA), computed tomography (CT), and fluorescence imaging) and also creates effective synergistic PTT/PDT of HER-2-positive breast cancer. GNSs protect ICG from photo-thermal damage and improve $^{1}O_2$ production, as well as increase their stability in the bloodstream and reduce blood clearance. To improve targeting efficiency, cytokine-induced killer (CIK) cells, which have the

tumor-homing ability, were used. These cells activate the immune system after intravenous administration, so the constructed nanoplatform acts against cancer through immunotherapy in addition to PDT and PTT [37, 43].

AuNFs possess branch structures and flower-like shapes along with absorbing light in the red deep region (600—900 nm). AuNFs have a high surface-to-volume ratio and tissue penetration compared with other forms of AuNPs such as spherical and rod-shaped and are used as an agent for imaging, nano-vehicle, and therapy [3, 44]. PDA-Ce6-GSH-AuNF is a multifunctional system capable of cancer synergistic therapy through PDT and PTT treatments, in which AuNFs with a diameter of about 80 nm and an absorption band in the vis-near infrared (Vis–NIR) range of 800–900 nm are used. AuNFs were synthesized using HAuCl4 salt at 0°C, through the template-free method, which has two steps. In the first step, HAuCl4 was reduced by ascorbic acid (AA) and Au seeds were formed. In the second step, through the seed-mediated approach, and using $NH_2OH{\cdot}HCl$ as a reducing agent, gold ions (Au^{3+}) were converted into gold nanoparticles. These nanoparticles are deposited on Au seeds (crystal nucleus) and branch structures of AuNFs are constructed. Then glutathione (GSH) molecules are anchored to the gold surface by their thiol group, and it is utilized as a linker for connecting chlorin e6 (Ce6) to AuNFs through the activated carboxyl group of GSH. Then Ce6-modified AuNFs were coated with polydopamine (PDA). PDAs are surface modification agents with high chemical and thermal stability and containing catecholamine functional groups with great adhesion properties, which create thin nanoscale layers on the surface of organic materials. Thin PDA layers increase cellular absorption of nanoparticles and their mucopenetration and also play a role in hydrophobic drug delivery, which is due to the hydrophilicity and zwitterionic properties they give to the material. PDA has an elevated absorption capability in the NIR region and high efficiency of energy conversion and creates red-shift adsorption, so as a photothermal agent, it can increase the PTT efficiency of the nanoplatforms. The nanoplatform was examined in vitro and in vivo, through a near-infrared (NIR) laser with a wavelength of 660 nm for PDT and 808 nm for PTT. Based on the results, the amount of Ce6 loaded in Au NFs was 14.0 wt.%, the singlet oxygen production efficiency by the designed nanoplatform was approximately 91.0% of free Ce6, and the photothermal conversion efficiency was 23.6% (7.0% more than free Au NFs). As regards that the antitumor efficiency was increased by combining PDT and PTT treatments, PDA-Ce6-GSH-AuNFs were considered as dual phototherapy agents [3].

Au NRs are one-dimensional anisotropic nanoparticles. Contrary to spherical gold nanoparticles, which have one LSPR band in the range of 520 nm, AuNRs have two LSPR bands; transverse LSPR (t-LSPR) with a wavelength in the range of 520 nm and longitudinal-LSPR (l-LSPR) with higher wavelengths in the range of the biological window (560–950 nm) and (1000–1350 nm). l-LSPR can be adjusted by changing the aspect ratio of AuNRs, and compared with the LSPR of spherical nanoparticles, AuNRs are more sensitive to environmental variations resulting from dielectrics. These features make AuNRs possess wide applications in biomedical, including LSPR-biosensing. AuNRs are one of the metal nanoparticles that are used in non-aggregation plasmonic colorimetric sensors as a mediator in the etching/growth process. This process alters the shape, size, and environmental dielectrics of metal nanoparticles, which follows the plasmon band changes. Based on the studies on Au NRs, gold nanoshells (nanocages, nanorod-in-shell, and nanoparticle-in-shell) and gold nanobipyramids (Au NBPs), **Figure 2**, have been used as PS in PDT and can produce singlet oxygen ($^1O_2$) [45–47]. Au NBPs are, like the Au NRs, one of the novel plasmonic nanoparticles, which have longitudinal dipolar plasmon

with a tunable wavelength from the visible region to the near-infrared. Au NBPs have higher shape and size uniformity and against Au NRs, which have curved or flat ends, Au NBPs contain two sharp end apexes, so Au NBPs could create higher regional electric field enhancements with more slender peak width. Au NBPs possess broad plasmonic usage in the areas of photocatalysis, sensing, and switching (such as plasmonic index-change-based sensing method, colorimetric and selective immunoassay, and electrochemical plasmonic switching), biomedical applications (PTT, PDT, real-time bioassays, as thermocycling-creating nanoreactors for rapid and quantitative real-time PCR, plasmon-enhanced fluorescence bioimaging agents, etc.), and plasmon-enhanced spectroscopies (PL), surface-enhanced Raman spectroscopy (SERS), etc.) [48].

Au NP creates antimicrobial effects through mechanisms, which include interaction with bacterial cell barriers, interaction with biomolecules such as enzyme activity inhibiting, DNA binding or interference in protein synthesis, bacteria-killing by photothermal effect, the redox imbalance, and increasing the effectiveness of antimicrobial photodynamic therapy (aPDT). According to studies, AuNPs do not cause the redox imbalance by making changes in the ROS level, but they affect the level of glutathione (GSH) [49]. According to reports, the mechanisms through which gold nanoparticles can increase the effect of aPDT are as follows: improving the relative distribution and production of ROS, and also, it can increase the amount of PS excitation and improving the efficiency of aPDT through conjugation with PS such as AuNPs-conjugated methylene blue (MB) against bacteria such as the mature methicillin-resistant *Staphylococcus aureus* (MRSA) biofilm [50–52]. By reducing photobleaching, AuNPs also increase the efficiency of photodynamic therapy. In a study in 2021, the effect of biosynthetic AuNPs-mediated mycelium of *Mucor plumbeus* on aPDT efficiency was investigated. Based on the observations of this study, biogenic AuNPs in combination with (Mb) methylene blue as PS can cause effective aPDT of both Gram-negative (*Escherichia coli*) and Gram-positive (*S. aureus*) bacteria. Biogenic AuNPs reduce the photobleaching speed of methylene blue by changing the kinetics of the photofading process [50]. In 2017, phototheranostic nanoagents (PTNAs) were designed, which possess biosynthesized AuNPs using *Syzygium cumini*'s fruit extract (ScAuNPs). In this study, the effects of ScAuNPs have been compared with chitosan-mediated AuNPs (ChAuNPs). According to the results, antioxidant efficacy, drug loading, fluorescence quantum yield (Q), singlet oxygen quantum yield, and antimicrobial PDT of ScAuNPs and their conjugated probes/nanoprobes were better than those of ChAuNPs [53].

Other forms of AuNMs are nanoclusters, **Figure 3**. Generally, metal nanoclusters (Au, Ag, Cu, etc.) have a different structure from metal nanoparticles, and subsequently, their characteristics, including their optical characteristics, change, too. These nanomaterials have several to 100 atoms and their size is less than 2 nm, which is comparable with the Fermi wavelength of electrons, which is usually less than 1 nm because as the size decreases, the continuous energy band of metals changes to a discrete energy level, which is associated with molecular-like electronic transitions (i.e., HOMO – LUMO transitions) in valence states. Metal nanoclusters (MNCs) could be categorized as water-soluble MNCs stabilized by biomolecules (proteins, peptides, DNA, etc.), and oil-soluble MNCs with easy crystallization, such as $Au_{25}(PET)_{18}$ (PET is phenethyl mercaptan), that is, oil-soluble mono-metallic NCs nobel metal nanoclusters (MNCs) have capping agents such as protein, DNA, and small organic molecules, good biocompatibility, and the ability to easily modify the surface characteristics. Also, they are good fluorescent labels, due to large stock

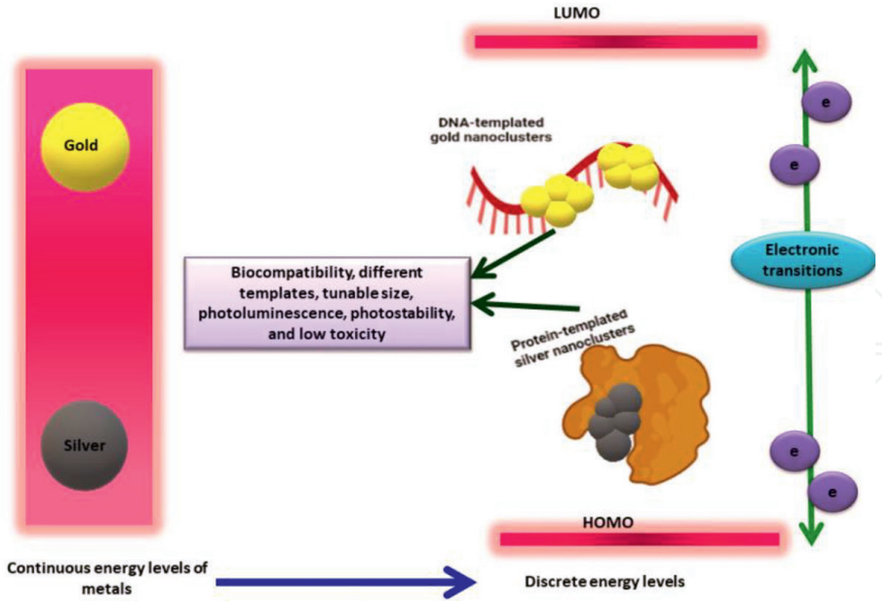

Figure 3.
Properties of AuNCs and AgNCs.

shift, size-dependent excitation and emission wavelength, and high optical stability [54–57]. Gold nanoclusters (AuNCs) consist of less than 100 gold atoms and have a size smaller than 2 nm, which is comparable with the Fermi wavelength of electrons (< 1 nm). AuNCs do not have localized surface plasmon resonance like gold nanoparticles because the electrons of the valence layer of AuNCs cannot move freely. AuNCs do not absorb plasma resonance in the visible region. The maximum fluorescence of gold nanoclusters is in the visible to NIR region, which is the appropriate wavelength for tissue penetration. Also, high photostability and great fluorescence lifetime in vivo conditions are other characteristics of AuNCs. Therefore, they have biomedical applications such as biosensing, bio-imaging, and therapy. AuNCs are used as inorganic PS in PDT. In 2014, in a study, a nanoprobe was designed in which Doxorubicin (DOX) was loaded in a nanocomposite consisting of AuNCs encapsulated in Zeolitic imidazolate framework-8 (ZIF-8). Due to their small size, AuNCs have limitations such as low enhanced permeability and retention (EPR) effect, short duration in blood circulation, and low accumulation in tumor sites due to fast clearance. To solve these limitations in this study, AuNCs were encapsulated in the inner of ZIF-8 and DOX in the channel of ZIF-8. This nanocomposite is pH-responsive and bifunctional so that it uses synergistic PDT/chemotherapy to treat breast cancer. And due to being pH-responsive, it is not released in neutral environments and normal cells are not affected. Their release occurs in acidic tumor sites, so the performance of PDT and chemotherapy is enhanced [29, 38, 54].

3.3 Silver-based nanomaterials

Due to the innate antibacterial properties of silver ions, it has been used by humans for many years and recently has been noticed in cancer therapeutics. According to studies, mechanism of Ag-based agents for therapy is irreversible apoptosis along with contacting Ag^+ to a thiol-rich protein that is located on the cell, and bacterial membrane leads to decrease of these proteins. So superficial contact is a factor that regulates antimicrobial effects. Ag^+ is restricted by a lack of stability

in the physiological body environment and target ability for tumors. So synthesis of nanoplatforms for Ag^+ accumulation in the diseased region and making synergistic therapeutic effects is vital [58]. Silver nanoparticles usually possess a size between 20 and 25 nm due to their high surface-to-volume ratio [12]. They have wide contact areas with viruses and bacteria, which subsequently improves the bactericidal performance. Therefore, the effects of silver nanoparticles on Gram-positive and Gram-negative bacteria depend on the size, dose, shape, and total surface area of the nanoparticle.

According to the studies, silver nanoparticles have high antibacterial effects on *Streptococcus mutans* in low concentrations, so their toxicity is reduced. Silver nanoparticles affect the morphology of *E. coli* and *S. aureus*, also they can alter the expression of some coating proteins such as (OmpA, OmpC, OmpF, OppA, and MetQ) and heat shock proteins (IbpA and IbpB). Ions released from silver nanoparticles can also have a biocidal effect [59]. Silver nanoparticles enhance photodynamic performance against the wide-broad spectrum of microorganisms bacterial and fungal species and including antibiotic-resistant strains, which is a public health threat all over the world. They can be used as carriers for PSs or as hybrids, composites, and conjugates with PSs [12, 60]. Silver core-mesoporous silica shell nanoparticles-containing HPIX (Hematoporphyrin IX dihydrochloride) is a hybrid PS that was synthesized in 2016 by Tevhide Ozkaya Ahmadov et al., [61] which exhibited significant photodynamic inactivation ability against MRSA (a multidrug-resistant strain of *S.aureus*) in such a way that its lethal efficiency increased up to six times [62]. As the size of silver nanoparticles decreases, their antimicrobial effect will be greater due to the increase of surface-to-volume, such that silver nanoclusters (AgNCs) with a size smaller than 2 nm exhibit stronger antimicrobial effects. Similar to AuNCs, AgNCs participate in photodynamic therapy. AgNCs have remarkable luminescence properties, biocompatibility, tunable size and photoluminescence, photostability, and low toxicity. Ag NCs have more antimicrobial capability than AuNCs, but their stability is lower than AuNCs, in a way that they don't preserve for a long time such as a few months while some AuNCs could preserve for more than a few months [63, 64].

The optical features of AgNCs are attributed to factors such as the quantum confinement effect, surface ligand effect, and the electronic transition between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), **Figure 3** [65]. Surface ligand affects the intramolecular and intermolecular control of nanoclusters, which are two kinds of continuous systems of nanoclusters control and both together adjust nanocluster systems. Intramolecular control points out the manipulation of metal–ligand compositions and bonding environment at the single-molecule level. Intermolecular control refers to changes in the aggregation pattern in amorphous or crystallographic forms. Ligand exchange and heteroatom alloying are methods for intramolecular control. Among the methods used for intermolecular control, we can mention cluster-based metal–organic framework, aggregation-induced emission, and intercluster metallophilic reaction. Based on the studies, manipulation of nanocluster crystallographic networks at the supramolecular level and the adjustment of intramolecular and intermolecular interactions make the nanoclusters become CIEE (crystallization-induced emission enhancement)-active or -inactive nanomaterials [62].

There are various methods for metal nanoclusters synthesis, among these approaches, the template-based method is suitable for the generation of metal nanoclusters, and they involve improving the stability, shape, and size-controlled and fluorescence tunability of metal nanoclusters. Templates or capping agents

can be dendrimers, proteins, peptides, and DNAs [50]. Bovine serum albumin (BSA) and human serum albumin (HSA) are the common proteins used as capping agents in the synthesis of nanoclusters (NCs). BSA has various functional groups such as -OH, -NH_2, -COOH, and -SH, which are involved in the synthesis of metal nanoclusters (MNCs) by creating steric stabilization. BSA has disulfide bonds that establish a covalent bond with the MNCs core through the sulfur. Also, the pH of the environment participates in the formation of nanomaterials and MNCs. For instance, BSA converts silver ions into silver nanoparticles at pH (6–8) and generates silver nanoclusters at pH higher than 11. Of course, the protein itself can also reduce the silver ions (Ag^+) without adding external reducing agents and turning them into silver nanoparticles and nanoclusters. BSA obtains various conformations, including -N (native), B (basic), A (aged), and U (unfolded), along with alterations of environment pH from neutral to alkaline that different nanomaterials are stable in some of these conformations [65].

AgNCs are also constructed with DNA templates in the way that this nanocluster has a high affinity to N_3 cytosine. The number of single-stranded cytosines installed in the primary and secondary structures of DNA (such as hairpin loops, i-motifs, and G-quadruplexes) controls the size and shape of AgNCs. Another feature of DNA-AgNCs is their resistance to photobleaching, which makes them have applications in nanophotonics and biosensing. One of the advantages of using oligonucleotides for the synthesis of AgNCs is the possibility of their synthesis with different sequences. AgNCs can exert antimicrobial effect through DNA intercalation and inactivation of type II topoisomerases. In 2016, Siamak Javani et al. investigated the antibacterial performance of fluorescent DNA-AgNCs, which has an inhibitory effect on the growth of Gram-positive and -negative bacteria in sub-micromolar concentrations. These DNA-AgNCs were synthesized with three types of oligonucleotide sequences named Seq1, Seq2, Seq3, and the absorption wavelengths of the resulting nanoclusters are 370 nm, 480 nm, and 560 nm, respectively, and their emission wavelengths are 475 nm, 572 nm, and 630 nm, respectively. The result of the antibacterial test for *E.coli* showed that Seq3 had more inhibitory effect than Seq2 and Seq1 showed the least inhibitory activity. Based on the results of this study, the factors that regulate the antibacterial performance of DNA-AgNCs are the amount of silver and factors such as sequence, structure, and Ag arrangement [66, 67].

4. PDT effects on immune system

PDT can lead to cell death through apoptosis, necrosis, autophagy, or proptosis. The type of cell death induced by PDT depends on the location of the PS and the amount of photodamage. Each of these cell death leads to the release of molecules such as alarmins or damage-associated molecular patterns (DAMPs), cytokines, growth factors, and other immunomodulating agents. Alarmins as immunostimulators are released after photooxidative damage that triggers innate immunity, which leads to the activation of adaptive immunity. They are detected by pattern recognition receptors (PRRs) that are expressed on immune cells, and subsequently, activate immune cells after DAMPs are attached to the PRRs. Similar to the lesion from infection and other tissue damage, PDT- mediated damage of tumor and endothelial cells is caused by release of inflammatory factors including arachidonic acid-derived metabolites arising from membrane lipids peroxidation (such as thromboxanes, prostaglandin, and leukotriene), high amount of cytokines such as the interleukin

(IL)-6, IL-1β, IL-2, IL-1β (possess a prominent role in PDT efficiency), MIP2 (CXCL2), tumor necrosis factorα (TNFα), acute phase proteins, pro-aggregatory and vasoactive mediator releasing (result in platelets activation and clotting cascade initiation). These factors lead to the migration of innate immune cells toward the tumor site for tumor cell elimination. The PDT immune cells from PDT-mediated damage include neutrophils, macrophages, natural killers (NK), and dendritic cells (DCs). Previous studies demonstrated that systemic neutrophilia is incorporated in immune-PDT interaction of tumor cells through various factors resulting from PDT-mediated damage, which can be mentioned in some cases, including: (1) Complement activation upon PDT is caused to release tumor tissue anaphylatoxins (such as C3a and C5a), subsequently, vascular permeability increasing and neutrophil infiltration. (2) Adhesion molecules such as E-selectin and ICAM1 for neutrophil adherence on tumor tissue and micro vessels, also adhesion to the subendothelial matrix by the β2 integrin receptors (3) Acute-phase proteins (APPs), which facilitate neutrophils migrate, mature neutrophil progenitors more quickly, and help them leave the bone marrow [68].

Macrophages as effector cells participate in immune-PDT of cancer cells. The release of HSP70 from tumor cells damaged by PTD will activate macrophages. Hsp70 is bound to PRRs (which are expressed on macrophages such as the toll-like receptors (TLRs) and as a result of this binding, TLR2/4 of macrophages is activated, followed by TNFα releasing. TNFα as a cytolytic cytokine leads to indirect tumor cell elimination. C3 and MBLs (mannose-binding lectins) opsonization of tumor cells provides their phagocytose possibility by macrophages, due to complement receptors expressed by macrophages could recognize opsonized agents. NK cells have also been interested in cancer PDT. According to reports, major histocompatibility (MHC) class I-related molecule (MICA) and Natural Killer Group 2D (NKG2D) ligands from photodamage are recognized by NKG2D receptors on NK cells and lead to activation of these receptors, consequently enhancing PDT-induced immunity. Dendritic cells (DCs) as antigen-presenting cells communicate between innate and adaptive immune systems. PRRs of DCs detect DAMPs, released by PDT-damage, following it to activate/mature dendritic cells leading to augment MHC class II and co-stimulatory factors expression, which will be associated with the presenting of antigens to T lymphocytes and activation of type 1, 2, and 3 of adaptive immunity. In type 1 immunity cytokines such as IL-12 and IFN-γ are expressed by $CD4^+$ T cells leading to the activation of the cytotoxic function of $CD8^+$ T cells. In type 2 immunity, $CD4^+$ T cells deviate to the Th2 phenotype, which is associated with cytokines expression such as IL-4 and antibody generation from B cells. According to studies demonstrated, $CD8^+$ T cells have a pivotal role in immune-PDT, in a way defects in these cells reduce the efficacy of PDT. Type 3 immunity induced by PDT arises from the increasing of T helper (Th17) cell numbers in the tumor-draining lymph nodes (TDLNs). Th17 cells are a subset of $CD4^+$ T cells that generate IL-17 cytokine that according to studies, this molecule has a significant role in neutrophils recruitment in TDLNs upon PDT and also neutrophils are effective in activated $CD8^+$T cells accumulation into tumor cells [68, 69].

5. Conclusions and perspectives

In the first parts of the paper, PDT as one of the applications of photodynamic function is addressed, then gold and silver nanomaterials-based PDT and finally, the challenges of metal nanomaterial-based PDT. Photodynamic is determined as

an action in which cells react with oxygen, light, and PS. Utilizin effective PS is an important agents in improving of PDT efficacy. There are different generations of PSs. Due to limitations of organic PSs, the attention toward metal-based nanomaterials for PDT has been increasing, due to their unique properties such as relatively narrow size, shape distribution, simplified functionalization, and consequently, active absorption, stability, and SPR. Metal nanomaterial-based PDT has challenges, including accumulation and long retention time of PSs, hypoxia and low PDT efficiency, low therapeutic penetration of light, brief half-life of $^1O_2$ and shorter diffusion amplitude in comparison with cell and organelles size, and metal nanomaterials toxicity. These challenges, especially nanotechnology risks, must be addressed in future studies. However, photodynamic techniques are frontier approaches for diagnosis and treatment of disease such as cancer and microbial resistances. Photodynamic applications and nanomedicine are the multidisciplinary fields that could design improved novel PSs with usage of different areas such as biology, physics, engineering, electronic, chemistry, informatics, pharmaceutic, and medicine. Therefore, PDT, especially along with other therapies (combination therapy), deserves attention in future research studies and clinical applications.

Acknowledgements

This work was supported by the Golestan University of Medical Sciences financial support (Grant number, 31-111679).

Conflict of interest

The authors of this project have no conflict of interest.

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