



# Applications of Gold and Silver Nanoparticles in Theranostics

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## Abstract

Nanotechnology sculptures the current scenario of science and technology. The word nano refers ‘small’ which ranges from 10 to 100 nm in size. Silver and gold nanoparticles can be synthesized at nanoscale and have unique biological properties like antibacterial, anti-fungal, antiviral, antiparasitic, antiplatelet, anti-inflammatory, and anti-tumor activity. In this mini review, we shall discuss the various applications of silver and gold nanoparticles (AuNPs) in the field of therapy, imaging, biomedical devices and in cancer diagnosis. The usage of silver nanoparticles (AgNPs) in dentistry and dental implants, therapeutic abilities like wound dressings, silver impregnated catheters, ventricular drainage catheters, combating orthopedic infections, and osteointegration will be elaborated. Gold nanoparticles in recent years have garnered large importance in bio medical applications. They are being used in diagnosis and have recently seen a surge in therapeutics. In this mini review, we shall see about the various applications of AuNP and AgNP, and highlight their evolution in theranostics.

**Keywords** Silver nanoparticle · Gold nanoparticle · Nanotechnology · Biomedical application · Evolution in theranostics

## Introduction

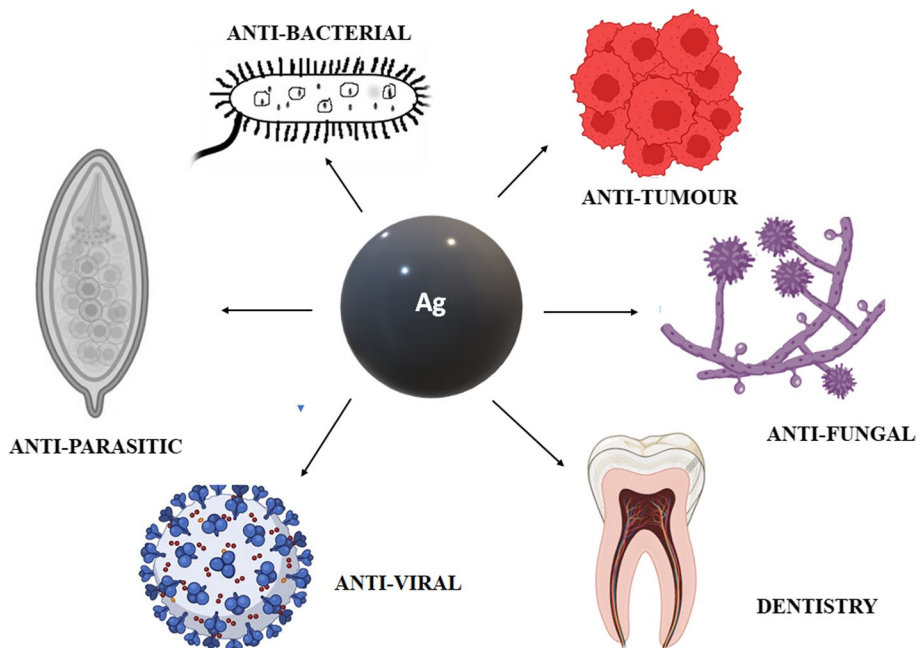
Nanotechnology is known as multifaceted field of science which deals with the particles at nanosized ranges from 10 to 100 nm. There are various types of nanomaterials used in fields of science and technology such as medicine, construction, agriculture, energy production, and food industry [1–5]. The characterizations of nanoparticles (NPs) are based on their shape (rod, triangular, polyhedral, octagonal, round) and among the various NPs, metal NPs has gained more attention in recent years due to their distinctive property. Their use is more primitive in comparison to other nanostructures and gold particles were used as medicine in India and China for ayurvedhic medicine preparation [6, 7]. Among metal

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NPs, gold and silver nanoparticles (AgNPs) have various potential application and uses due to their application in allied disciplines and biomedical properties. AgNP is used in cleansing up the environmental pollution, medical imaging techniques and also exhibit more in the biomedical field because of large surface area to volume ratio [8–10]. AgNP is a powerful disinfectant and antibacterial agent and is used as a topical silver sulfadiazine cream as an antibiotic for treating burn wounds. It also shows antibacterial activity with garlic, cinnamon extract and is reported to have anticancer, anti-inflammatory activity etc., as shown in Fig. 1 [11–15]. The recent advancements and developments of gold nanoparticle (AuNP) in medicine and in theranostics have also gained attention. They are being used in diagnosis and have recently seen a surge in therapeutics. AuNP has a deep connection with chemistry, and in the Roman era(735BC) they were used in art decorations [16]. It has been identified that gold nanoparticles are used in various field of sciences such as diagnosis, cancer treatment, antibacterial and anti viral agent [17]. Noble metal are those which are defiance to oxidation at higher temperatures and corrosion. Some of the metals used are palladium, osmium, ruthenium, rhodium, iridium, platinum, copper, silver, gold, etc. These metal nanoparticles play a prominent role in the development of nanobiosensors in point of care testing, gene delivery, gene detection, intracellular trafficking targeting, cancer treatment, preventing tuberculosis, HIV, keratitis, imaging and therapeutics [18]. Metal nanoparticles can produce excessive reactive oxygen species, protein damage, inflammation which leads to toxicity, and it can also produce hyperthermia locally. The fundamendal principle is that it exhibits photocatalytic and photothermal effects by which under the light the metal nanoparticles gets excited at different wavelength [19]. In this review, we will discuss about the various applications of AgNP and AuNP in the field of theranostics and biomedical science.



**Fig. 1** Applications of silver nanoparticles

## Biological Properties of Silver Nanoparticle

### Antibacterial Agent

Multi-drug-resistant bacteria have become very prominent these days which has limited the resources for controlling infections using conventional therapies, such as, antibiotics, radiation etc. AgNPs is used as a superior antibacterial agent and has been found to be effective against a broad spectrum of vancomycin resistant strains in Gram-positive and Gram-negative bacteria [20–24]. Silver ions released by the AgNPs attaches to the thiol (SH) group of the sulfur and hydrogen present in the bacterial proteins and inhibits the bacterial growth [25–27]. AgNPs are potent against both anaerobic and aerobic bacteria and it functions by obstructing the bacterial electron transport chain system and precipitating the bacterial cellular proteins [28–30]. As AgNPs have larger surface area to volume ratio, it shows better efficiency [22, 31] and the mechanism of action are as follows,

1. The silver ions in AgNPs inhibits the function by reacting with phosphorous present in the DNA and sulfur containing proteins present in the bacterial membranes [32].
2. A nanometer scale silver provides firm attachment to the cell membrane and penetrates the bacterial cell wall [33, 34].
3.  $\text{Ag}^+$  ions in AgNPs causes cell death by bombarding the electron transport chain in bacterial mitochondria [35].
4. Continuous detachment of silver ions in the bacterial cell from AgNPs with an environment of lower pH produces free radicals, induces oxidative stress, and enhances the antibacterial activity [27, 36].
5. AgNPs attaches to the bacteria and it penetrates inside the cell wall, further leading to death [31].

The shape, size, and concentration of the AgNPs determines the antibacterial efficacy. Studies state that enlarging the surface area of AgNPs can enhance the antibacterial activity [37]. Researchers have demonstrated that AgNPs possessed 50% inhibition activity against multidrug resistant bacteria (MDR)- *Staphylococcus aureus* and *E. coli* at a very low concentration of 20  $\mu\text{g}/\text{ml}$ . At a further high concentration of about 40  $\mu\text{g}/\text{mL}$ , it exhibited an efficient inhibition of both microorganisms. In another study, biosynthesized AgNP using marine macroalgae *Padina* species observed a good bacteriostatic activity against pathogenic Gram-positive organism like *Bacillus subtilis*, *Staphylococcus aureus* and Gram-negative bacteria like *Pseudomonas aeruginosa*, *E. coli*, *Salmonella typhi*. AgNPs with the concentration of 1mg/ml exhibited a higher sensitivity against *Pseudomonas aeruginosa* with diameter of zone of inhibition of  $13.33 \pm 0.76$  mm and *Staphylococcus aureus* of  $15.17 \pm 0.58$  mm respectively, where as the negative control possessed 0.00 mm. [38]. In another study, a comparative analysis was done with small AgNPs and PEGylated AgNPs of different molecular weight against a prime pathogen *Staphylococcus aureus*. In this study, 12 different sizes of AgNPs have been synthesized with a size range of  $29.7 \text{ nm} \pm 0.02$  to  $35.5 \pm 0.02$  nm in three different pH of 10, 11 and 12. Excellent bactericidal activity was brought in by the PEGylated AgNPs with the zone of inhibition of about 29 mm at a pH 10. This was because PEG possessed a high hydrophilic property that eliminated more water and terminated the microbes [39]. Veerasamy et al have observed antimicrobial activity in the Green synthesized AgNP using *Malia Azedarach* at the concentrations of 25, 50, 75, 100  $\mu\text{g}/\text{ml}$  in which highest zone of inhibition was observed at

100 µg/ml as 21 mm and 12 mm for *Pseudomonas aeruginosa* and *Bacillus subtilis* respectively [40].

## Antifungal Agent

Prolonged use of antifungal drugs leads to multidrug resistance especially for *Candida* species [41]. AgNPs coated reverse osmosis membrane exerted better antifungal activity against *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida tropicalis* [24]. AgNP exerts antifungal property by interrupting the cell membrane and inhibits the normal asexual reproduction process by destroying the membrane integrity [42]. Mallmann *et al.*, reported that AgNPs prepared by bio synthesis using SDS as stabilizer and reducing agent as ribose exhibited increased antifungal activity against *C. albicans* and *C. tropicalis* [43]. Additionally, AgNPs suppresses the growth of *Aspergillus niger* by 70% and *Cladosporium cladosporoides* by 90 %. Increasing the concentration of nanosilver minimizes the fungal growth in a dose dependent manner. AgNPs coated in cotton has shown antifungal activity against *Aspergillus sp* and the zone of inhibition was observed at  $14.33 \pm 3.51$  mm [44]. A study was done with biosynthesized AgNPs using *Malva parviflora* and leaf extract of *Malva parviflora* (LEMP) to monitor the antifungal activity against *Alternaria alternata*, *Fusarium oxysporum*, *Fusarium solani* and *Helminthosporium rostratum*. With an average diameter of 50.6 nm, the AgNP mitigate the mycelia growth of *H. rostratum* at 88.6%, *A.alternata* at 83.0%, *F.solani* at 81.1% and *F.oxyspoum* at 80.7% where as the LEMP showed growth inhibition at 65.3% for *F.solani*, 54.7% *F.oxyspoum*, 53.6% *H.rostratum* and 45.6% for *A.alternata* [45]. Another study discussed about the pathogenic fungus which affects the quality of crops. To overcome this, mycosynthesized AgNPs using *A. niger* fungal isolate to invade against plant pathogenic fungi was utilized. At a concentration of about 10 µg/ml, AgNPs showed inhibition of 91.0% for *Fusarium oxysporum*, 97.3% for *Aspergillus flavus*, and 93.75% for *Penicillin digitatum*. This is because on treatment with  $Ag^+$ , the DNA ruins its ability to replicate, thereby resulting in dormant expression of ribosomal subunit proteins and the enzymes needed for ATP production. [46]. A synergistic antifungal activity of Epoxiconazole and *Lingustrum-lucidum* leaf extract against *Setosphaeria turcica* showed the inhibitory percentage of 50 % against the organism at 170.20 µg/ml concentration. At a ratio of 8:2 and 9:1 synergistic antifungal activity was seen in combination with epoxiconazole. This method gave a new perspective for the integrative control of plant pathogen [47].

## Antiviral Agent

Metal NPs like gold or silver exhibit antiviral activity against broad spectrum of virus by direct interaction with nanomaterial and viral surface proteins and reduce the infectivity of the viral cultured cells. Recent studies have shown that metal NPs are effective antiviral agents against HIV 1, Respiratory syncytial virus, HSV type1, monkey pox virus, Tacaribe virus and influenza virus [48–52]. AgNP coated with poly (N-vinyl-2-pyrrolidone) showed antiviral property against HIV1 by interacting with gp 120 [53]. AgNPs and polysaccharide coated AgNPs ranging from 10–80 nm size was potent against monkey pox virus of Poxviridae family by blocking the virus – host cell binding and penetration [52]. AgNP at non-toxic concentration are used effectively to inhibit tacaribe virus (TCRV) of Arenaviridae family by inactivating the viral particles at their initial entry [54]. Saadh *et al.*, observed that AgNP integrated with epigallocatechingallate (EGCG) and doped with zinc

sulphate showed a potent antiviral activity against Avian influenza A virus H9N2. At a concentration of 50  $\mu\text{M}$  EGCG, it reduced the titre of AI H9N2 ( $\log\text{EID}_{50}/\text{ml}$  was 4.2). By increasing the concentration of EGCG  $>50 \mu\text{M}$ , it did not show any enhanced antiviral effect. Effective result was obtained by combining EGCG with zinc sulphate showing  $\log\text{EID}_{50}/\text{ml}$  ( $1.5 \pm 0.6$ ) [55]. Another study was on synthesizing AgNPs using *Lampranthus coccineus* and *Malephora lutea*. This study possessed that the hexane nanoextract of *L.coccineus* showed 50% inhibition against HAV-10 virus, HSV-1 virus and CoxB4 virus with concentration 11.71 ng/ml, 36.36  $\mu\text{g}/\text{ml}$  and 12.74  $\mu\text{g}/\text{ml}$  respectively [56].

## Antiparasitic Agent

Saad and colleagues synthesized silver and copper NPs and studied the antiparasitic activity which showed remarkable decrease in the oocyte availability in *Cryptosporidium parvum*. They have also studied that AgNPs are effective against parasitic infection of *Entamoeba histolytica* and *Cryptosporidium parvum*. AgNPs expresses larvicidal activities against *Aedes aegypti* and *Culex quinquefasciatus* [57]. Allahverdiyev et al. demonstrated a study to assess the effects of AgNPs over the biological parameters of *Leishmania tropica*. AgNPs attack the parasites by impairing the lipophosphoglycan and glycoprotein 63 present in the surface of the parasite which is responsible for the infection. The study revealed that AgNPs have the potential to inhibit the promastigote's proliferation activity. And further, the AgNPs in the presence of increased UV light hinders the endurance of amastigotes in host cell [58]. A study on biosynthesis of AgNPs using Corn cob nanoxylan as a reducing and stabilizing agent observed a minimum inhibitory concentration ( $\text{IC}_{50}$ ) of 25  $\mu\text{g}/\text{mL}$  against *Leishmania amazonensis* promastigotes [59]. In an *in vitro* study of AgNPs against *Entamoeba histolytica* trophozoite, the result showed a mortality percentage of 46.2 %, 42.4 % for 75  $\mu\text{g}/\text{ml}$  and 46.2 %, 46.7 % for 100  $\mu\text{g}/\text{ml}$  of concentration after 24 h and 48 h incubation respectively [60].

## Anti-inflammatory Agent

Silver-based NPs is powerful in preventing the bacterial infections and inflammation [61]. Intra-peritoneal injections of AgNPs in animal models showed decrease in the degree of post operative fibrous adhesions. Hebeish et al., have done the *in vivo* efficacy of albino rats' and grouped the 24 albino rats into 4 groups. Group 1 was the negative control and given 1 ml of saline. Group 2 & 3 rats were administered with two different AgNPs concentration of 250 ppm and 124 ppm respectively. Group 4 was the reference drug administered with indomethacin at concentration of 20 mg/kg rat. After one hour, all animals were given a sub planter injection of 1% carrageenan solution in 0.1ml of saline over the right hind paw and 0.1 ml saline in left hind paw. After four hours of administration, rat's both the paws were excised and weighed separately. The oedema percentage showed that the synthesized AgNP could significantly decrease in degree of rat oedema. The oedema percent of 250 ppm concentration of AgNPs gave the same effect as the standard drug indomethacin. Thus, it was indicated that AgNPs could reduce inflammation significantly [62]. Shensha et al., made a study on *Nigella sativa* oil mediated AgNPs to assess the anti-inflammatory activity in male Wister rats which showed inhibitory concentration at 54.40% (1 h) and 60.30% (5 h) with the dose of 0.3 mg/kg bodyweight [63]. Researchers have biosynthesized AgNPs using *Selaginella myosurus* aqueous extract which showed significant

inhibition of paw edema of Wistar rats of 44.30% (1h), 57.60% (5 h) and 60.50% (5 h) for the concentration 0.1, 0.2 and 0.4 mg/Kg (body weight) respectively [64].

### Antiplatelet Agent

Thrombotic disorders have become the remarkable problem in the medical field. Anti-coagulant and thrombolytic therapy can lead to many bleeding complications. Recently Dakshayan et al. demonstrated the role of *Selaginella bryopetris* (Sanjeevini) plant extract supported AgNPs (SPE @AgNP) in platelets. Platelet aggregation assay was performed in platelet rich plasma with ADP and Epinephrin as agonists. SPE @AgNP inhibited ADP only and not the Epinephrin. Platelet exhibits its major role in arresting the bleeding in addition to the coagulation factors and they tend to aggregate at the injury site forming a platelet plug and it is vulnerable to the collagen present in endothelium [65]. Thrombin, ADP, epinephrine, thromboxane, thrombin, platelet activating factors etc. are the agonist that activates the platelets [66]. Formation of thrombus in arteries and vein occurs when platelets get hyperactivated. Thus, SPE @AgNP was used in the treatment of thrombotic disorders as a superior antiplatelet agent along with its anticoagulant activity [67]. Additionally, Shrivastava *et al.*, demonstrated that AgNPs inhibited the integrin mediated platelet functional responses like aggregation, adhesion, secretion to immobilized fibrinogen or collagen [26].

## Therapeutic Application of Silver Nanoparticle

### Wound Dressing

AgNPs are used in wound dressing, in case of toxic epidermal and necrolysis, severe burns etc. AgNPs takes about 3.35 days on an average to heal the wound and the bacterial load decreases in wound area with no further effects [68]. AgNPs works more effectively when compared with 1 % silver sulfadiazine for superficial burns. In case of deep burns, AgNPs and 1 % silver sulfadiazine does the same work and AgNPs promotes the restoration of intact epidermal barrier but do not form any new tissue [69]. The application of biopolymer based biomaterial increases because of biocompatibility, biodegradability, non-immunogenicity and nontoxicity. The biopolymers used are gelatine, collagen, keratin, natural rubber proteins, polysaccharide. Collagen is a natural biopolymer and the usage of biopolymers in wound healing showed a better positive output in the clinical trials. Collagen sponges and glycosaminoglycans act as a double layered artificial skin and heals the wound. These act as a good carrier for AgNP to release the drug in a sustained manner [70]. Hasari *et al.*, reported that silk based novel bilayer wound dressing material with gelatine is less toxic to skin cell than other wound dressing available and it also promotes the wound healing by increasing the collagen production [71]. Studies have shown that chitosan and keratin have wound healing effects and antimicrobial activity. Chitosan is effective for the treatment of chronic periodontitis [72]. Scientists have emerged with worlds first AgNP based commercially available wound dressing material (ACTICOAT: Smith and Nephew, UK) that covers the huge area of burns and increases the wound healing activity [73]. A study was done with konjac glucomann silver nanoparticle (KGM/AgNP) a composite sponge which possessed a better wound

healing capacity and also exhibited good cytocompatibility. By animal experiments they have confirmed the activity of wound healing, and on the day 14, KGM/Ag3 wound healing capacity was increased to 99 % [74].

### Silver Impregnated Catheters

The prevalence of central venous catheter (CVC)–related bloodstream infections were about 80,000 cases annually. However, the use of CVC in hospitals of the USA was around 5 million for 1 year [75]. Patients with tumour, intracerebral haemorrhage, subarachnoid haemorrhage were implanted with external ventricular drain (EVD) catheters usually for the therapy of acute hydrocephalus. The EVP catheters were significantly used for monitoring the draining CSF and intracranial pressure. Previously catheters were impregnated with antibiotics that decreased the colonization rates [76], which led to bacterial resistance. Therefore, a new trend of silver coated catheters was used in clinical field, in which the silver ions bind with an inert ceramic zeolite by the help of inorganic silver powder. Recent studies described that, there was a remarkable reduction in the colonization rate in silver impregnated CVC [77]. In a previous study, *A.baumannii* was made to form a biofilm to mimic the *in vivo* infection conditions and the CVC was coated with polydopamine and tested for the bactericidal activity. By surface characterization with field emission scanning electron microscopy, water contact angle (CA), Raman spectroscopy the results showed that dopamine coated AgNPs had a CA value of  $49.1 \pm 0.3$  [78]. Fichtner et al. conducted retrospective clinical analysis to see the contrasting efficacy between silver coated EVD catheters and standard non coated catheters. There was a significant reduction in the positive culture of CRI. Bacterial colonization was likely to be 4 times in EVD catheters in comparison to the standard non coated catheters. Another study showed that the growth of *Staphylococcus aureus* reduced in the silver coated EVD catheters [79].

### Silver in Orthopaedics

Benchmark treatment for the arthritic disease is the artificial joint replacement. The use of bone cements like poly methyl methacrylate (PMMA) resulted in high rate of infection when integrated in the bones. Nanotechnology has evolved in the field of orthopaedics and trauma. Hence, nano silver coated bone cement resulted in outrageous antibacterial activity against broad range of bacteria including methicillin resistant *Staphylococcus aureus* (MRSA). Taken further, the nanoparticle did not show any cytotoxicity. Ultra high molecular weight polyethylene (UHMWPE) was used for the artificial joint replacement but the only disadvantage was with the wear and tear and associated debris generation, which led to inflammation and failure of joints in the body. This major problem was overcome by integration of AgNPs with bone cement. This protocol consequently reduced the polymer debris formation [20, 80]. The rate of infection was reduced by adding the AgNPs to the outer layer of the implants. A group of scientist demonstrated that there was an effective resistance to *Escherichia coli* by exposing it to modified titanium film. It also had a role in reducing the pin tract associated infections [69, 81]. Orthopaedic infections resulted in high morbidity when osteoblast like cells, and bone marrow mesenchymal stem cells were exposed to AgNPs and showed maximum inhibitory concentration of 25 µg/ml [82].



## Silver Surgical Meshes

Prosthetic mesh is not commonly used implanted devices for pelvic reconstructive surgery and hernia repair. The incidence of mesh associated infections ranges between 0.6% and 8.0% [83, 84]. In accordance to the one million herniorrhaphies there were around 30,000–50,000 prosthetic mesh infection in the USA [85]. Multiple antibacterial coatings were used on the medical devices such as urinary catheters, central venous catheters and surgical meshes to reduce the infection rate [86]. To reduce the occurrence of prosthetic mesh infections in the post pelvic and hernia surgery, nanocrystalline silver particles with polypropylene was used [87]. The antimicrobial activity of silver nanoparticle relies in the electrical state of the ions. Silver is biologically active in its soluble form as  $\text{Ag}^+$ . Commonly used topicals like silver sulfadiazine, silver nitrate, has silver in the form of  $\text{Ag}^+$ . Topical silver formulations were used two to twelve times a day in burn areas because of the rapid inactivation of silver ions with chloride or organic ions present in the wounds. In comparison to  $\text{Ag}^+$ ,  $\text{Ag}^0$  does not form complex resulting in halt in rapid inactivation of microbes [88]. Nanocrystalline silver has decreased one million nosocomial infections in a year with the patients implanted with prosthetic material [89]. Cohen *et al.*, reported that polypropylene integrated with nanocrystalline silver particle (NCSP) showed that silver particles circulated inside the mesh and produced a zone of inhibition and higher inhibition efficacy against *Staphylococcus aureus*. The zone of inhibition increased in a dose dependent manner with increase in the concentration of silver [90]. NCSP also holds the property of anti-inflammatory agent. Secondary mechanism of NCSP is to repress tumour necrosis factor  $\alpha$  and interleukin (IL)-12 and initiate inflammatory cell apoptosis [91].

## Dentistry

AgNPs pops up as a promising agent used in dentistry. This property is because of their integration of antimicrobial property in dental biomaterials [92]. The major mechanism is by liberating cationic silver and its oxidative potential [93]. Using AgNPs in dentistry, is effective against multidrug resistant bacteria and for its prophylactic action. AgNPs are used in different streams like preventive dentistry, orthodontics, endodontics, periodontics and in oral dentistry. AgNPs inhibit the growth of *Staphylococcus aureus*, *Streptococcus mitis*, *Streptococcus gordonii* biofilms. Additionally recent study states that AgNPs exert its antibacterial activity against *Streptococcus sobrinus*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Streptococcus sanguinis*, *Enterococcus faecalis* and *Actinomyces actinomycetemcomitans* [94]. Incorporation of AgNPs into polymers used as denture base and tissue conditioners in stomatitis have showed superior antimicrobial activity and capacity to fight against oral infections. Another study stated that modified denature base acrylic combined with AgNPs at 20.0 wt.% showed antifungal property [95]. AgNPs with smaller diameter size exerts good biofilm inhibition when compared with larger particles. Biological synthesis of AgNPs using neem, onion, and tomato with size measuring 26.2 to 33.3 nm showed antimicrobial activity against *Staphylococcus aureus* because of the high concentration of flavonoids and terpenoids in it [96]. Pérez-Díaz *et al.*, reported that AgNPs inhibited the growth of planktonic *Streptococcus mutans* and killed the *Streptococcus mutans* biofilms. Thus, AgNPs play a significant role in dentistry and prevents dental caries [97]. Decrease in adhesion of biofilm and production of lactate by microorganism is seen in AgNPs treated with titanium disc -based composites [98]. A



nano bacteriostatic agent silver Nano fluoride had inhibited the growth of *Streptococcus mutans* and it could be used once a year, easy to use, and had a better cost benefit ratio. This was a superior replacement for sodium fluorine [99]. Titanium micro implants with biopolymer coated AgNPs (Ti-BP-AgNp) showed largest zone of inhibition of  $50.58 \pm 4.88 \text{ mm}^2$  for *Streptococcus mutans*. The zone of inhibition for *S. sanguinis* was  $27 \pm 3.01 \text{ mm}^2$  and for *A. actinomycetemcometans* showed a smaller zone of inhibition of about  $25 \pm 3.06 \text{ mm}^2$  with the control showing no zone of inhibition [100].

## Cancer Theranostics

Cancer is a global menace and is caused by environmental effects and mutations in genes which activates the sequence of events in molecular level and leads to tumour formation. [101]. There are two major causes for cancer, they are external and internal factors. The external factors include radiation, viruses, chemical exposures, environmental conditions etc. [102]. Internal factors comprise the mutations, hormones and immune conditions which trigger the process of carcinogenesis [103]. Chronic low dose exposure to oxidative stress is also known to be a contributor for cancer onset by circumventing apoptosis [104]. Many studies showed that AgNPs get localized inside perinuclear space of cytoplasm and endo lysosomal compartment cells by entering cells through endocytosis [105, 106]. AgNPs affect the respiration of cells and produce reactive oxygen species (ROS). As AgNPs are harmful to cells and proceeds to oxidative stress, damage of DNA, trigger the apoptosis and damage of mitochondria to cancer cells [107–112]. Studies showed that AgNPs can affect the activity of vascular endothelial growth factor which are involved in angiogenesis [113]. Theranostics is the mixture of diagnostics and therapy. Biosynthesized AgNP possess theranostic applications as it holds the anti-cancer property and used in targeted drug delivery and bioimaging vehicle [114]. It is a cost effective, safe, simple and eco-friendly approach [115]; the different applications of AgNPs in anti-cancer therapy is summarised in Table 1.

## Silver Nanoparticle in Imaging

### Silver Nanoparticle as Photoacoustic Imaging

In the field of biomedical applications, research has increased in the area of designing and delivery of NPs to the specific organ. To know whether the nanoparticle has delivered to the diseased tissue and to also know about the intended function of NPs, a new combination of photoacoustic imaging modality and custom designed nano system has emerged [157, 158]. The main principle behind this is, first, the object will absorb light, then absorbed light energy will develop as heat and finally because of thermoelastic expansion, acoustic waves will be release out [159]. Photoacoustic imaging was first proposed by Oraevsky, for the use of biomedical applications [160]. AgNPs possess strong optical absorbance and scattering properties and are used as contrast agents for imaging therapies. With the light of wavelength 800 nm and radiation, the NP's injected 1cm deep in *ex vivo* pancreatic tissue could be detected using ultrasound imaging and photoacoustics. First mode is, AgNPs are engineered to target the tumour site specifically to the leaky blood vessels of the tumor and the reduced the rate of clearance due to lack of functional lymphatic vessels, and will retain the AgNPs [161]. The second one is, at the site of tumour, the AgNPs gets conjugated with

**Table 1** Antitumor effects of AgNPs

S.No.	Types of Silver nanoparticles Used	Model used	Outcome	References
1.	Green synthesis of AgNPs using Ganoderma neo-japonicum Imazeki	Breast cancer cell lines	AgNP increased the production of hydroxyl radical and reactive oxygen species by inhibiting the cell viability. They play a prime role in apoptosis by activation of caspase 9 and DNA nuclear fragmentation.	Gurunathan <i>et al.</i> , [116]
2.	Green synthesis of AgNPs using <i>Escherichia fergusonii</i>	Breast cancer MCF 7 cell lines	Cytotoxicity effects of bio synthesized AgNP reduced the activation of LDH, increases the ROS production and results in apoptosis.	Gurunathan <i>et al.</i> , [117]
3.	Green synthesis of AgNPs using sucrose	Malignant skin melanoma (HT144 cell line) and squamous cell lung carcinoma (H157 cell line)	Observed a prominent antitumor activity against vincristine and methotrexate.	Nazir <i>et al.</i> , [118]
4.	Green synthesis of AgNPs using <i>Taraxacum officinale</i>	Liver hepatocellular carcinoma in HepG2 cell line	Possess an enhanced activity against the commercial AgNP and in increased cytotoxic effects against HepG2 cell line	Saratale <i>et al.</i> , [119]
5.	Chemical biosynthesis of AgNPs using phycocyanin extracted from <i>Nostoc linckia</i> as reducing agent	Human breast adenocarcinoma	Observed a significant cytotoxic activity against MCF-7 cell line with the inhibitory concentration (IC <sub>50</sub> ) of about 27.79±2.3 µg/ml	Naggar <i>et al.</i> , [120]
6.	Green synthesis of AgNPs using <i>Sargassum vulgare</i>	Human myeloblastic leukaemia in HL60 and HeLa cells	Prevents carcinogenesis related with irradiation by inhibiting lipid peroxidation – mediated reactive oxygen species generation which leads to apoptosis.	Govindaraju <i>et al.</i> , [121]
7.	Green synthesis of AgNPs using <i>Piper longum</i> leaf	Hep 2 cell line	Observed effective cytotoxic effect of 94.02% at 500 µg/ml due to formation of ROS.	Jacob <i>et al.</i> , [122]
8.	Green synthesis of AgNPs using <i>Inonotus obliquus</i> extract	Human lung cancer in A549 cell line and breast cancer in MCF -7 cell line.	Cell lines shows significant cytotoxic effects.	Nagajyothi <i>et al.</i> , [123]

**Table 1** (continued)

S.No.	Types of Silver nanoparticles Used	Model used	Outcome	References
9.	Green synthesis of AgNPs using <i>Commelina nudiflora</i>	HCT-116 Colon cancer cell line.	AgNP showed less toxicity when compared with AuNP and inhibitory concentration ( $IC_{50}$ ) was 100 $\mu$ g/ml.	Kuppusamy <i>et al.</i> , [124]
10.	Green synthesis of AgNPs using <i>Melia dubia</i> leaf	Human breast cancer cell line (KB)	The inhibitory concentration ( $IC_{50}$ ) was 31.2 $\mu$ g/ml.	Kathiravan <i>et al.</i> , [125]
11.	Green synthesis of AgNPs using <i>Dimocarpus longan Lour</i>	H1299 lung cancer cell line.	Possess inhibitory effect with ( $IC_{50}$ ) value of $5.33 \pm 0.37$ $\mu$ g/ml and suppress the growth of H1299 tumours in SCID mice.	He <i>et al.</i> , [126]
12.	Cisplatin (cis-diamminedichloroplatinum II) bound bio AgNPs using <i>Penicillium</i> , <i>Fusarium</i> and <i>Aspergillus</i> .	Prostate cancer cell line (PC-3).	Decreases the toxic effects and increases the efficacy against human prostate cancer	El-Sheikh <i>et al.</i> , [127]
13.	Green synthesis of AgNPs using root extract of <i>Erythrina indica</i>	Breast and lung cancer cell line (MCF-7 and HEP G2).	Viability of the cells decreased with increase in concentration of AgNP. At 25 $\mu$ g/ml, the viability percentage is $23.89 \pm 0.39$ for MCF-7 cell line and $13.86 \pm 0.95$ for HEP G2 cell line. This root mediated synthesis plays a role in cancer chemotherapy and chemoprevention.	Sre <i>et al.</i> , [128]
14.	Green synthesis of AgNPs using <i>Acalypha indica</i> leaves extract.	Human breast cancer MDA-MB-231 cells	Four different concentrations were used, such as, 1, 10, 50, 100 $\mu$ g/ml, in which 100 $\mu$ g/ml AgNP exposed toxicity to some extent.	Krishnaraj C <i>et al.</i> , [129]
15.	Green synthesis of AgNPs using leaf extract of mistletoe <i>Dendrophthoe falcata</i> (L.f) Ettungsh	Human breast carcinoma (MCF-7 cells)	At merest dosage of 5 $\mu$ g/ml, of fabricated AgNP they observed the enhanced cytotoxic effect. This concentration is the $IC_{50}$ value.	Sathishkumar <i>et al.</i> , [130]
16.	Green synthesis of AgNPs using <i>Datura innoxia</i> leaves.	Human breast cancer (MCF-7 cell line)	The inhibitory concentration at 50% ( $IC_{50}$ ) was 20 $\mu$ g/ml. It also seizes the cell cycle phase, suppresses the growth, finally induces apoptosis and exhibits the antiproliferative activity against MCF -7 cell line.	Gajendran <i>et al.</i> , [131]

**Table 1** (continued)

S.No.	Types of Silver nanoparticles Used	Model used	Outcome	References
17.	Green Synthesis of AgNPs using <i>Clinacanthus Nutans</i> leaves extract.	Oral squamous cell carcinoma cell line (HSC-4)	Observed a prominent cytotoxic effect at the concentration of $1.61 \pm 0.14 \mu\text{g/ml}$ by repressing the release of Bcl-2 protein.	Yakop <i>et al.</i> , [132]
18.	Green synthesis of AgNPs using <i>Pimpinella anisum</i> seeds	Human neonatal skin stromal cells (hSSCs) and colon cancer cells (HT115)	Observed lower cytotoxicity for bio-synthesized AgNP of about 51.39% in comparison with chemically synthesized one that showed 85.45%. And it is useful in pharmacological applications for producing nanodrugs.	AlSalhi <i>et al.</i> , [133]
19.	Biosynthesized AgNPs using aqueous fruit extract of <i>Chaenomeles sinensis</i> (C5)	Human breast cancer cell line (MCF-7)	At concentration of $0.01 \mu\text{g/ml}$ , the viability percentage of cells was remarkably reduced.	Keun Hyun Oh <i>et al.</i> , [134]
20.	Green synthesis of AgNPs using <i>Saccharomyces boulardii</i>	Human breast cancer cell line (MCF-7)	$\text{IC}_{50}$ of bio-synthesized AgNP was about less than $10 \mu\text{g/ml}$ . This indicated that AgNP with low concentration exhibited almost 80% of inhibition of the cancer cells. They observed no significant changes in the higher concentration ( $10\text{--}100 \mu\text{g/ml}$ )	Kaler <i>et al.</i> , [135]
21.	Green synthesis of AgNPs using <i>Indigofera tinctoria</i> leaf extract	Lung cancer cell line (A549)	$\text{IC}_{50}$ value of AgNP-tinctoria was $71.92 \pm 0.76 \mu\text{g/ml}$ . This is because of the NPs induced ROS.	Vijayan <i>et al.</i> , [136]
22.	PVP coated AgNPs	Human lung cancer cell line (Alveolar cell line A549)	1. $\text{Ag}^+$ with $0\text{--}10 \mu\text{g/ml}$ and AgNP with $0\text{--}20 \mu\text{g/ml}$ concentration exhibited similar toxic effects and a decrease in mitochondrial function. 2. Study showed that oxidative stress was induced by both AgNP and $\text{Ag}^+$ by correlating with geno and cytotoxicity.	Foldbjerg <i>et al.</i> , [137]

**Table 1** (continued)

S.No.	Types of Silver nanoparticles Used	Model used	Outcome	References
23.	Green synthesis of AgNPs using aqueous extract of <i>Phyllanthus emblica</i> (PE) fruit.	Laryngeal carcinoma cells (Hep2 cell line)	Observed a potent cytotoxic effect, the IC <sub>50</sub> value of PE alone was 30 µg/ml and PE-AgNP was 20 µg/ml.	Rosarin <i>et al.</i> , [138]
24.	Green synthesis of AgNPs using <i>Padina tetrastromatica</i> seaweed extract	Human breast cancer cell line (MCF-7)	With increased concentration, the percentage of inhibition increased. The bio-AgNP showed a value of IC <sub>50</sub> as 86.7 µg/ml and AgNP value was 200 µg/ml. The observed cytotoxicity effect of AgNP was because of caspase 3 mediated apoptosis.	Selvi <i>et al.</i> , [139]
25.	Green synthesis of AgNPs using leaves of <i>Vitex negundo</i>	Human colon cancer (HCT15 cell line)	Proliferation of HCT-15 was inhibited with a concentration of 20 µg/ml (IC <sub>50</sub> ) at 48h incubation. They exhibited a antiproliferative effect by seizing the G <sub>0</sub> /G <sub>1</sub> - phase and induced programmed apoptosis.	Prabhu <i>et al.</i> , [140]
26.	Green synthesis of AgNPs using <i>Artemisia turcomanica</i> leaf extract	Gastric cancer (AGS cell line)	The IC <sub>50</sub> value of bio-synthesized AgNP was 4.88 µg/ml and commercial AgNP showed a value of 6.37 µg/ml. This study inferred that least concentration of bio-AgNP was sufficient to inhibit the cell growth when compared with commercial AgNP.	Mousavi <i>et al.</i> , [141]
27.	Green synthesis of AgNPs using <i>Bacillus licheniformis</i> in tumour bearing mice.	Dalton's lymphoma ascites (DLA cell line)	Observed a prominent decrease in tumour volume from 7.3ml to 2.6ml in the group of mice treated with AgNP with the concentration of 500 µg/ml in about 15 days.	Sriram <i>et al.</i> , [142]
28.	Chemical synthesis of AgNPs.	Glioma (U251 glioblastoma cells)	AgNP exhibited better inhibition over U251 glioma cells in comparison to AuNP. The IC <sub>50</sub> of AgNP was 75.9 µg/ml.	Liu <i>et al.</i> , [143]
29.	Metal silver and PVP coated AgNPs on tumor bearing mice	Lymphoma	70% and 60% of mice survived at the day 35 with the metal silver and PVP AgNP administered at day 0.	Lara-Gonzalez <i>et al.</i> , [144]

**Table 1** (continued)

S.No.	Types of Silver nanoparticles Used	Model used	Outcome	References
30.	Poly vinyl pyrrolidone -coated nano silver (PVP-AgNP) and bare nano silver (AgNP)	Human hepatoma cell line (HepG2 cell line) and mice.	1. AgNP caused more DNA damage to HepG2 cells than PVP-AgNP, whereas PVP-AgNP possessed more chromosomal aberration in comparison to AgNP. 2. At the highest dose of 250 mg/mL, they observed no inhibitory effects in the bone marrow cells of mice.	Wang <i>et al.</i> , [145]
31.	Green synthesis of AgNPs using curcumin derivative (ST06)	Cervical cancer in HeLa cell line and EAC (Ehrlich Ascites carcinoma) tumour bearing mice.	1. At a concentration of 1 µg/ml of ST06 and 1 µg/ml of ST06-AgNP, 50% of the cells were killed in a HeLa cell line. 2. Inferred that at the concentration of 5 µg/ml (ST06-AgNP) intraperitoneally inhibited the tumour growth in a tumour bearing mice which did not affect the body weight.	Murugesan <i>et al.</i> , [146]
32.	Green synthesis of AgNPs using <i>Spinacia oleracea</i> leaves.	Myoblast cancer (mouse C <sub>2</sub> C <sub>12</sub> cell and in zebra fish)	1. AgNP showed 100% inhibition of growth at low concentration of about 20 µg/ml and AgNP, at a concentration of 100 µg/ml exhibited 20% viability of cells, whereas the plant extract did not possess any significant cytotoxic effects against C <sub>2</sub> C <sub>12</sub> cell. 2. In zebrafish embryo, AgNP was more toxic and exhibited 100% mortality at concentration of 3 µg/ml and AuNP showed the 100% mortality only at higher concentration of 300 mg/ml. Moreover, plant extract did not cause any mortality.	Ramachandran <i>et al.</i> , [147]

**Table 1** (continued)

S.No.	Types of Silver nanoparticles Used	Model used	Outcome	References
33.	Green synthesis of AgNPs using poisonous plant <i>Cleistanthus collinus</i> extract.	Lung cancer cell line (A549 cell line) and mice.	1. Poisonous plant at a finite dosage was used as an anticancer agent. The inhibitory concentration (IC <sub>50</sub> ) was found to be 30 µg/ml. 2. <i>In vivo</i> histopathological findings in mice treated with bio-synthesized AgNP did not show any edema or inflammation in the organs. Thus, it could be used for diagnostic and therapeutic purposes.	Kanipandian <i>et al.</i> , [148]
34.	Green synthesis of AgNPs using <i>Teucrium polium</i> leaf extract	Human gastric cancer (MKN45 cell line)	The IC <sub>50</sub> value of T. polium-AgNP is 68.2 µg/ml after 48h exposure.	Hashemi <i>et al.</i> , [149]
35.	Green synthesis of AgNPs using <i>Albizia adianthifolia</i> leaf extract.	Lung cancer (A549 cell line)	Observed significant cytotoxic effect and the cell viability percentage was 79% and 27% in the concentration of 10 µg/ml and 50 µg/ml, respectively.	Gengen <i>et al.</i> , [150]
36.	Green synthesis of AgNPs using aqueous extract of <i>Punica granatum</i>	Lung cancer (A549 cell line)	Possessed cytotoxic effect to cancer cells but not to the normal cells. Potent cytotoxicity i.e., 50% growth inhibition was observed after 48h at a concentration of 5 µg/ml.	Annu <i>et al.</i> , [151]
37.	Green synthesis of AgNPs using walnut fruits ( <i>Juglans regia</i> )	Breast cancer (MCF-7)	Observed a significant cytotoxic effect at the concentration of 60 µg/ml as 70% and 42% for AgNP and extract, respectively.	Khorrami <i>et al.</i> , [152]
38.	Green synthesis of AgNPs using <i>Aspergillus niger</i>	Human colon cancer (HT29 cell line)	Highest cell viability percentage was at 10 µg/ml and lowest at 160 µg/ml with exposure time of 24–72h by exhibiting ROS mediated apoptosis.	Chengzheng <i>et al.</i> , [153]
39.	Green synthesis of AgNPs using alcoholic extract of <i>Argemone Mexicana</i> leaves.	Cervical cancer (SiHa human cervical cancer cell line)	Observed a decrease in percentage of cell viability (70–80%) with the concentration of 100µg/ml.	Jha <i>et al.</i> , [154]



**Table 1** (continued)

S.No.	Types of Silver nanoparticles Used	Model used	Outcome	References
40.	Green synthesis of AgNPs using <i>Pseudomonas aeruginosa</i>	Thyroid cancer (TCL1 cell line)	IC <sub>50</sub> value was observed as 48.5 µg/ml by increasing the lipid peroxidation, decreasing the mitochondrial membrane potential, reducing antioxidants and finally cell condensation took place.	Yang <i>et al.</i> , [155]
41.	Green synthesis of AgNPs using the extract of red sea weed <i>Pterocladia capillacea</i>	Human hepatocellular carcinoma (HepG <sub>2</sub> cell line)	Infers that the level of cytotoxicity increased with higher concentration. Untreated cells were used as negative control. The 50% of cell inhibition (IC <sub>50</sub> ) occurred at 3.7 µg/ml of concentration.	El Kassas <i>et al.</i> , [156]

antibodies and bind to the antigens present. By localizing the AgNPs at the tumour site, it provides photoacoustic contrast with normal tissues thereby useful in *in vivo* examination of tumour [16].

## Gold Nanoparticles and Their Applications

Over in the last half century, AuNPs have been developed in many ways. Synthesizing AuNPs is now more reliable and are high in yields. These AuNP have distinct traits, namely size and shape dependent electrical and optical features, surfaces that can be changed with ligands containing functional groups. With the help of these functional groups to hold the ligands, and other biomolecules such as antibodies, proteins, etc. the newly formed gold nanoconjugates possess a wider range of research in therapeutics [16]. AuNP have provided useful materials for various biomedical applications, such as material crystallizations, programmed assembly, conversion of NPs into dimers and trimers and then to DNA templates, detection methods and bioelectronics. In diagnosis of a disease, the process of binding between the analytes and AuNPs, the physicochemical properties of AuNPs can be altered. We shall see about the various applications of AuNP and highlight their evolution in theranostics [162] in the sections mentioned below.

## Medical Uses of Gold

Gold has been used in medicinal practices for many decades including Chinese and Indian medicines. They were mainly used for the treatment of arthritic diseases. But it was later found that nephrotoxicity was caused by gold due to the prolonged exposure. Hence, they were not used in medical practices until researchers developed a new compound called auranofins and aurothioglucose [163]. Yao et al, made a comparative study of Gold clusters using Bovine serum albumin as template, Gold clusters using glutathione and Au nanoparticles with large particle diameter in both *in vitro* and *in vivo*. Gold nanoparticles acts by suppressing the proinflammatory mediators which is produced by lipopolyschharide. In comparing the above three, Au clusters with glutathione as template produced a better anti-inflammatory effects thus it is one of potent nanodrug for treating Rheumatoid arthritis [164]. Osteoarthritis is kind of the arthritis which is attributed by swelling, stiffness and joint pain. Researchers studied the use of AuNPs for improvising the delivery of chondroitin sulfate. Chondroitin sulfate is one of the drug for treating osteoarthritis. The combination of Chondroitin sulfate and AuNP augment the production of extracellular matrix and proliferation of chondrocytes [165]. Since they are non-toxic, they are vividly used in biomedical applications as well as in gene and drug delivery. The optical intensity of AuNP has been subjugated for polynucleotide detections. Gold consists of a dielectric core and can be used suitably to make nanoshells, which are very useful in Surface enhanced Raman spectroscopy (SERS). AuNP has the ability to aggregate upon themselves when they interact with proteins. One of the basis for the quantitative method of colorimetric determination of proteins were the sudden colour change in the solution. This process helped in a better accurate result for many analytical methods including ELISA. AuNP is used in photothermal therapy. This is used in tumor therapy and infectious diseases. AuNP tend to become hot when they reach their maximum absorption in visible or near infrared region at the corresponding light wavelength. This kills the cells that are located around or inside the target cells. Today controlled and direct damaging of the tumor tissues is possible in

cancer thermotherapy using laser radiation. But there are a lot of questions regarding its biodistribution, blood stream circulation, pharmacokinetics and toxicity. There are numerous research groups which use AuNP in their projects. There is a vast difference in the experiments, functionalizing methods, and dosages. Due to this, there has been major inconsistency with the data and the kinetics of biodistribution for toxicity estimation. Due to the development of efficient medical tools, AuNP has provided technologies for the functionalization of molecules providing stabilization *in vivo*. AuNP is now widely being used as problem solvers in bioimaging. [166]. AuNP have a great future in the medicine field, but one important concern is their safety level towards humans and environment. The AuNP toxicity depends on their physical dimensions and surface chemistry. Studies based on cytotoxicity of AuNP in human cells was done and the research showed that AuNP are nontoxic upto 250 mM, while ionic gold showed cytotoxicity at 25 mM. Lot of similar results were produced using AuNP in therapies [167].

## **Gold Nanoparticles for Cancer Theranostics**

Cancer therapy has grown rapidly in the past few years. But surgery with chemoradiotherapy still remains the go to procedure for fighting malignant cancer. Nanotechnology has recently been in the main topic in medical research, and many NPs have been studied for cancer therapy. The color of AuNP changes when there is increase in their size. Because of this unique property AuNP can be used in detecting various biomolecule and easily identify the tumor targets that are accumulated in vitro and in vivo. The most commonly used metal in cancer theranostics are gold and iron oxide because of their structure stability, variability of the size, controlled release and low toxicity during cancer theranostics [168]. Table 2 shows the different anti tumor effect of AuNPs.

AuNPs are used for both cell imaging and CT imaging in vivo. They are used mainly because they act as an alternative to X-ray based CT machines. They are used because of their better absorbent coefficient, easy attachment to the moieties and better body tolerance. AuNP has a great X-ray attenuation because of their high concentration and smaller size. Due to this it becomes easier to diagnose cancer with imaging [171]. The tissue absorption is very weak for light of wavelength >650 and <2,000 nm and that is the reason the NIR light is used for deep tumor imaging. AuNPs are the NIR-active probe for imaging the cancer cells in our body which is used for whole body scans. AuNPs are conjugated with anti-EGFR antibodies and used as a contrast agent in tumor imaging [172, 173].

## **Gold Nanoparticles for Cancer Therapy**

### **Photothermal Therapy (PTT)**

Gold has shown promising results in various cancer treatment such as photodynamic and photothermal therapies. This photothermal therapy is done through converting absorbed light into heat by nonradiative process. There are two main process:

1. The heat which is absorbed from energy conversion is given to the surrounding environment through the phonon relaxation within 100 ps.
2. A meticulous process of heating the electron and being cooled by the surrounding medium takes place, when the rate of heating is higher than the rate of cooling.

**Table 2** Antitumor effects of AuNPs

S.No.	Type of Gold Nanoparticles used	Model used	Outcome	References
1.	Green synthesis of AuNPs using <i>Commelina nudiflora</i>	HCT-116 Colon cancer cell line.	AuNP at high concentration of 400 µg/ml showed 90% cell death in HCT-116 cell line and the inhibitory concentration (IC <sub>50</sub> ) was 200 µg/ml.	Kuppusamy <i>et al.</i> , [124]
2.	Green synthesis of AuNPs using <i>Acalypha indica</i> leaves extract.	Human breast cancer MDA-MB-231 cells	Four different concentrations were used - 1, 10, 50, 100 µg/ml, higher toxic effects were showed by AuNP at 100 µg/ml possessing 40 % of cell toxicity. This exhibited AuNPs as a novel anticancer agent which could be used for the human breast cancer.	Krishnaraj <i>C et al.</i> , [129]
3.	Biosynthesized AuNPs using aqueous fruit extract of <i>Chaenomeles sinensis</i> (C5)	Human breast cancer cell line (MCF-7)	Observed a significant cytotoxicity at >25 µg/ml.	Keun Hyun Oh <i>et al.</i> , [134]
4.	Green synthesis of AuNPs using <i>Indigofera tinctoria</i> leaf extract	Lung cancer cell line (A549)	IC <sub>50</sub> value of AuNP- tinctoria was 56.62±0.86 µg/ml. This was because of the NPs induced ROS.	Vijayan <i>et al.</i> , [136]
5.	Chemical synthesis of AuNPs	Glioma (U251 glioblastoma cells)	The IC <sub>50</sub> of AuNP was 116.3 µg/ml which was less potent than AgNP.	Liu <i>et al.</i> , [143]
6.	Gold nanoparticles with hibiscus and curcumin extracts	Human colorectal cancer (HCT 116) and Michagen Cancer Foundation-7 (MCF-7)	The IC <sub>50</sub> of AuNP, Hibiscus against HCT-116 and MCF-7 was found to be 5.80±0.91 µg/ml and 3.67±0.75 µg/ml and for AuNP-Curcumin was 4.94±0.84 µg/ml and 3.91±0.65 µg/ml respectively.	Akhtar <i>et al.</i> , 2022 [169]
7.	Gold nano bioconjugates with Elephantopus Scaber (linn.) hydro methalic extract.	Michagen Cancer Foundation-7 (MCF-7), A-549 cells, Squamous cell carcinoma (SCC-40) and Human colon cancer cell lines (COLO- 205)	The 50 % cell growth inhibition (GI <sub>50</sub> ) for AuNP was found to be < 10 µg/ml against MCF-7 cell line where as in A-549, SCC-40, COLO-205 was 33.0, 28.3 and 24.7 µg/ml respectively. Thus AuNP was one of the good antiproliferative agent.	Shinde <i>et al.</i> , 2022 [170]

To use the photothermal therapy, a continuous wave laser is overlapped maximally with the AuNP resonance band. To achieve PTT using gold nanospheres the resonance of Continuous-Wave visible lasers should be in the visible region. This method can be used in treatment of shallow tumors. Recently, the development of antibody targeted gold nanospheres were done to primarily target EGFR on squalor carcinoma cells [172]. Researchers have developed new type of nanomatryoshkas which consists of PEG stabilizing ligands and concentric gold silica layers. In comparison to the existing gold-silica nanoshells which is approximately 150 nm, these nanomatryoshkas could facilitate higher concentration in tumors due to their ability to infiltrate the smaller AuNP in to the tissue. The survival rate of TNBC model was lesser than 1000 mm<sup>3</sup> which significantly decreased the size of the tumors by gold nanomatryoshkas and this was superior than the conventional silica-gold nanoshells. The results were taken under irradiation with a CW laser emitting 3W/cm<sup>2</sup> at a wavelength of 808 nm [174].

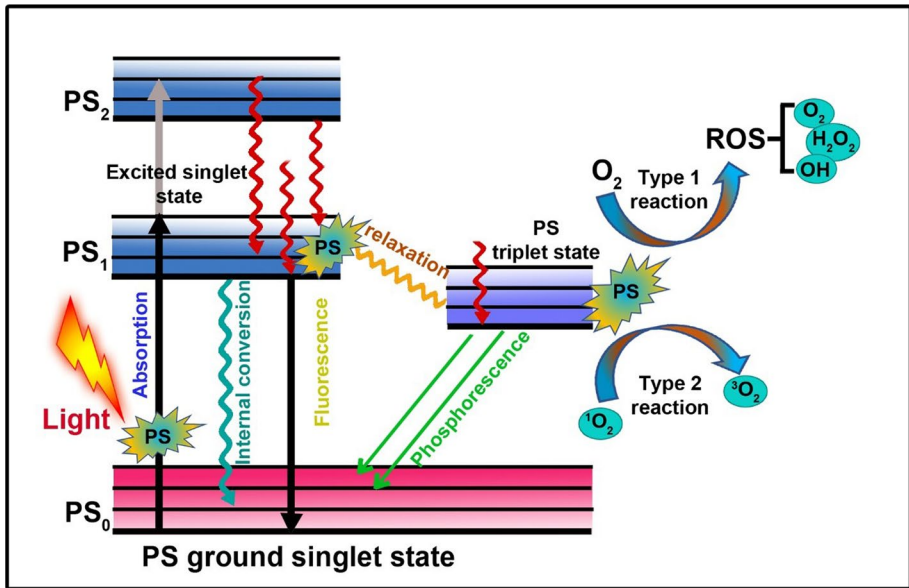
### Photodynamic Therapy (PDT)

Photo synthesizers tend to convert the surrounding oxygen into a toxic reactive oxygen species when they are stimulated under a specific wavelength that might destroy the malignant cells in the surrounding proximity, which is now known as cancer PDT [175, 176]. To treat deeply buried tumors, AuNP exert PDT over NIR light activation. In addition, the incorporation of various photosensitizers with NIR active property into the AuNP can also be done with low dosages of organic photosensitizers and lasers with short exposure irradiation for PDT. When tested under an 808 nm laser, CS-AuNR-ICG NSs at the same time produced reactive oxygen species and hyperthermia, which attained complete inhibition of tumor growth in xenografted mice. In comaprison to PTT or PDT the combined therapy showed a drastically better therapeutic effectiveness [177]. The principle of photodynamic therapy is explained in Figure 2. Nanobiosensors has emerged as great tool in diagnosing cancer. Figure 3 describes the principle of nanobiosensor. Functionalized gold nanoparticles are immobilized on a template which can detect the analytes (proteins, toxins, antibodies, disease amrkers, cells etc.) with high specificity and sensitivity. The combination of analyte and recognition element which is attached to the gold nanoparticles gives a signal (heat, light, fluorescence, electrochemical change-current, potential and conduction, sound) which is converetd into measurable elctrical or optical signal. The amplifiers then amplify those signals to make them measurable using electronics [178].

### Use of Gold Nanoparticles in SARS-cov-2 Virus

#### COVID Test

AuNP can be used as a test kit to find out whether a person is infected by the virus or not. As we know the existing test kits require atleast 12 h to find whether the person is infected or not. In these critical 12 h the person might come in contact with another infected person and acquire the virus. With the help of AuNP we can reduce both the amount of time required for testing a person and the amount needed to spend for testing. These AuNP based assay test is done in an molecular level i.e. it checks the RNA of the person. This helps in accurate result for the identification of the virus. If this is the case, then it might prove positive for everyone because it'll be helpful in finding out who is infected and can



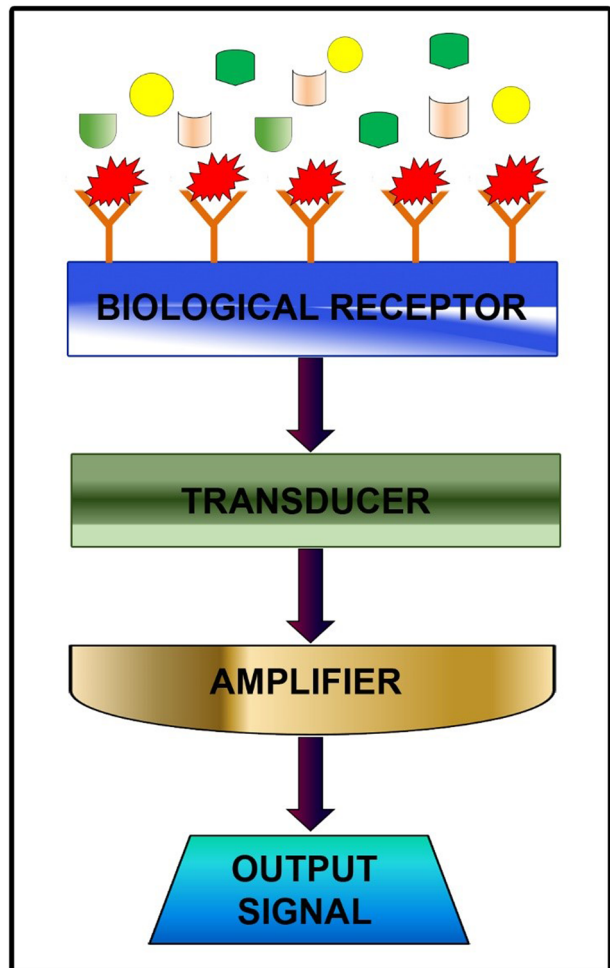
**Fig. 2** Mechanism of Photodynamic therapy. PDT takes place through type I and type II reactions that can create ROS for killing the cancer cells

treat the person well before it gets worsened. Because the test kits available in the market doesn't give the results at the earliest time, this methodology can be helpful. [179].

## Covid Vaccines

The endurance of the human for the past 3 years become an dispute due to the outbreak of Covid 19. Severe Acute respiratory syndrome-Cov-2 (SARS-CoV-2) affects both humans and animals. Many researchers were in demand of developing Covid vaccines by collaborating with pharma companies. WHO reported on 9th June 2020 that among 136 vaccine candidates, 16 where nano based vaccines which are under clinical trials [180]. S proteins are the chief goal for the Corona virus vaccine production as it plays a role in its pathogenesis. Chen et al made a study using synthetic viral like particles as an effective vaccination tool in an avian model of Corona virus infection. Synthetic virus like particles were prepared by incubating the 100 nm gold nanoparticles in the optimal viral protein concentration solution. This enhanced the antibody titer, increased the lymphatic antigenic delivery, splenic T-cell response and decreased the infection symptoms. In comparison with the whole inactivated virus, synthetic viral like particles produced a better antiviral protection [181]. NPs in general are most preferred when it comes to destroy a deadly virus. This is mainly because of their nano size and the flexibility to alter a nanoparticle according to the virus. Covid 19 virus, an enveloped shape virus, which ranges from 50nm - 150nm in diameter has undergone many mutations. The exterior of this virus is covered by proteins in form of spikes which infects our cells. The genetic material of this virus is said to be ssRNA. This is one of the main reason for using a nanoparticle in killing this virus. Nanoparticle has the tendency to mimic a virus. This a good thing because it gives us the ability to directly attack the virus without affecting the nearby cells. The main

**Fig. 3** Mechanism of Nanobiosensor. The biological receptor contains the recognition element that can specifically bind with the target molecule and convert them into measurable signal through the transducer. The signal gets amplified and recorded as output



path of these virus is to attack our respiratory system by binding with the cells in the respiratory system and affecting them with the help of protein spikes. There many ways to stop this from happening. As of now there are no confirmed therapeutic ways to destroy these viruses with the help of NPs. All of these are still in clinical trials. But it is well known that NPs is the way to destroy the virus efficiently [182].

### Current Limitations

As we have discussed above, AuNP gives us the possibility to be used in cancer diagnostics and therapeutics. But it is foolish to not consider the other side of the coin. These NPs might have side effects on health of the human beings. There are many studies in the cytotoxicity of AuNP, toxic effects of size, efficacy, response of NPs, biodistribution. But these researches give out contradicting results leaving us in a challenging situation. Absence of solid information on the effects of NPs could have serious effects and a negative impact on



human health. Chaves et al., studied toxicity of gold nanoparticles by *in vitro* using HT- 29 and HepG2 cell lines and *in vivo* using Wister rats. For this study, reserchers used 10 ppm of 10, 30 or 60 nm gold nanoparticles for the experiments. AuNP increased the production of ROS in cells at 16 h and at the 32 h the overproduction was normalised. As a result of *in vivo* studies, AuNP produced an increase in protein carbonyl groups formation and lipid peroxidation, which was measured by Thiobarbituric acid reactive substance (TBARS). Gold content got accumulated in liver, intestine, spleen, faeces,urine and kidney of rats [183]. Li et al., proposed that AuNP obstructs the proliferation of cells by dysregulating the cell cycle genes and it also affects the genomic stability and DNA repair [184]. This findings shows that there is a side of bane for gold nanoparticles and it is very important to evaluate the toxicity of any metal and metaloxide nanoparticles [185].

## Conclusion

There are various metal NPs that as a predominant application in various fields of science. In which AuNP and AgNP has a vast range of application such as antimicrobial, antiinflammatory, diagnosis, anticancer agent and also has therapeutic activity such as in dentistry, orthopedics, cancer therapy, etc.,. which are mentioned above. Most of the researches are still in clinical trials. Some of them were already applied for treatment and diagnosis. Future research is necessary to conclude the safety aspects of nano silver and gold.

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**Code Availability** Not Applicable

## Declarations

**Ethics Approval** • The manuscript is not be submitted to more than one journal for simultaneous consideration.

- The submitted work is original and should not have been published elsewhere in any form or language (partially or in full).
- A single study is not split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (i.e. ‘salami-slicing/publishing’).
- Results are presented clearly, honestly, and without fabrication, falsification or inappropriate data manipulation (including image based manipulation). Authors have adhered to discipline-specific rules for acquiring, selecting and processing data.
- No data, text, or theories by others are presented as if they were the author’s own (‘plagiarism’). Proper acknowledgements to other works have been given.

**Informed Consent** Not applicable

**Consent to Participate** Yes

**Consent for Publication** Yes

**Conflict of Interest** The authors declare no competing interests.

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