A REVIEW SYNTHESIS AND BIOLOGICAL EVALUATION OF PLANT-BASED METALLIC GOLD NANOPARTICLES

Abstract

Nanotechnology has become a trending area in the field of science and technology. It has made great advances with the development of functional, engineered nanoparticles.The better advancements made towards the synthesis of nanoparticles using plant materials has(have) become a major focus of researchersbecause of their advantages including high stability and loading capacity.Recently, zinc oxide nanoparticles have drawn the attention of several researchers owingto their several biological applications including anticancer and antimicrobial activities. Different techniques have been employed for the production of gold nanoparticles due to their elaborated applications in different interdisciplinaryfields. The synthetic procedure of plant-based nanoparticles has attracted a keen interest of various reserachers(researchers)as the syntesis is comparatively fast, safe,and light and can be followed under basic room conditions without the requirement of any advanced synthesis requirements. Every part of the plants can be used for the synthesis of nanoparticles. Gold nammoparticles(nanoparticles)play a pivotal role as the most active, environment friendly, and biocompatible towards a greener approach. In this review paper, we report highlighted about the various plants extract, which have been used for the synthesis of gold nanoparticles and their biological evaluation based on previous year's research and scientific papers and journals, and articles.

Keywords: Synthesis, characterization, gold nanoparticles, anticancer activity, antimicrobial activity.

Background

These days there are many research activities on nanoparticles, which are going on all over the world. These particles that is(are) intermediate between bulk materials and isolated atom sized materials in the range of 1 to 100 nm. The uses of these are not restricted but are involved in various agricultural and pharmaceutical applications [1]. NPs can be extensively divided into two groups, organic NPs which include carbon NPs (fullerenes, carbon nanotubes, etc.), and inorganic NPs consist of magnetic NPs, noble metal NPs (like silver and gold), and semi-channel NPs (like titanium oxide and zinc oxide). There is a developing enthusiasm for inorganic NPs i.e., metallic NPs (silver, gold and copper) as they give predominant material properties for functional versatility. Metallic NPs are themost encouraging and wonderful biomedical operators. Among metallic NPs, Silver,

Aluminum, Gold, Zinc, Platinum, Titanium, Palladium, Iron and Copper have been widely used. They exhibit unique properties that differ fromthose of the same material in bulk formNPs. Generally, show bio comp ability, strong adsorption ability and ease of surface modification. The application of these gold NPs is traced even in the 16th century for both therapeutic and re-coloring there is a further scope to grow ecologically cordial procedures through green amalgamation and other organic methodologies. Nowadays the nanoparticles are being synthesized from metal and from non-metallic materials. However, when it comes to the biological application of nanoparticles, silver, and gold are the most preferred metals [2-3].

Synthesis of nanoparticles is an area of interest for many researchers and is synthesized through various physical and chemical methods. During the chemical production of nanoparticles the toxic and hazardous risks are involved and are a potential threat to the environment, as well as it is expensive [4]. The science of the synthesis of nanoparticles using biological means is a newly emerging area and gained significant attention from researchers. The green approach uses living organisms or the bi-products of them, which act as a reducing agents as well as stabilizers. It is being vastly utilized for the production of nanoparticles [5-6] especially for the synthesis of silver, gold, iron, zinc, palladium, etc.

Metallic nanoparticles have the most favorable antibacterial properties because of their huge surface area to volume ratio, and it is the foremost interest of researchers because of microbial resistance, which is growing against metal ions, resistant strains development, and antibiotics. Amongst all noble metal nanoparticles, silver nanoparticles attained many interests because of theirbest conductivity, chemical stability, anti-viral, antifungal, anticancer and antibacterial activities that can be consolidated in the form of complex fibers [4, 6].

Main Text

Brief History of Gold Nanoparticles

Nanoparticles and nanoparticulate materials exist from ancient times. Although some of these nanoparticles have been synthesized deliberately (or not) by humans, it is also likely to find some natural-synthesized nanoparticles. On the other hand, humans have also synthesized nanoparticles for a long time. Actually, it is possible to find some different nanostructures in old glasses, statues or pottery pieces. However, the first mention toofnanoparticles may be awarded to Michael Faraday, who was probably the first person who synthesized deliberately gold nanoparticles by reducing Na[AuCl4] with an aqueous solution of Na[AuCl4] with phosphorous in carbon disulfide (Figure 1).

On February 5, 1857, Faraday delivered a Lecture of the Royal Society entitled "Experimental Relations of Gold (and other Metals) to "Light" in which he exposed his conclusions about extremely finely divided metal particles in suspension. Progressing towards later times in 1959, Richard Feynman, an American physicist from the Technological Institute of California (Caltech), presided a conference in the American Physical Society entitled "There's Plenty of Room at the Bottom", in which he pointed the possibility of manipulating the atoms directly one by one, with a Nano metric (Nanometric) precision. Subsequently, Feynman received the Physics Nobel Award in 1965. Both the scientific and technological worlds have become very interested in nanoparticles and other kinds of nanostructures. In the recent timesdifferent governments are moving towards investing huge capitals for the better esrtablishment(establishment) of a new domain titled "Nano world". For instance, the EEUU budget during the 2005-2010 periods was about 2.500 million euros, and the current UE budged since 2007 has reached 3.300 million euros. Thus, the resulting nanoparticle properties are sometimes mostly due to the large material surface area, which overcomes the small bulk material contributions. For instance, nanoparticle suspensions are possible because of the particle surface interaction with the solvent, which is strong enough to exceed [7-9].

The difference in densities ~~which~~can result in a material either floating or forming precipitates insidethe medium. Different other size-dependent parameters include different optical properties (i.e. gold nanoparticles are red and turn todark(todark)purple when aggregating) or superparamagnetic behavior at room temperature in magnetic materials, among others. As well as size, theshape is also a crucial parameter which (that) becomes necessary to control when studying nanoparticle properties. Gold nanoparticles exhibit various sizes ranging from 1 nm to 8 μm and they also exhibit different shapes such as spherical, sub-octahedral, octahedral, decahedral, icosahedral multiple twined, multiple twined, irregular shape, tetrahedral, nano triangles, nano prisms, hexagonal platelets, and nano rods (Figure2).

Recent advances of Gold nanoparticles

High surface/volume ratio and thus the huge number of surface gold atoms create much increased surface chemical reactivity and enhance chemisorption's of molecules such as CO and H_2 has been widely studied for applications in catalysis AuNPs[8-9]. Possess properties such as dielectric function, electrical conductivity, and inert properties to oxidation to allow them to be used in applications as sinter inks, selective coatings, data storage, single electron conductivity, and quantum devices Surface Plasmon Resonance (SPR) is one of the most remarkable properties of AuNPs[10-11]. SPR is a physical concept describing the collective oscillations of conduction band electrons in

the electromagnetic field. SPR will occur when a particle is small enough that its size is comparable to the wavelength of light. This property provides a new platform for applications as sensors for thedetection of many targets including biological, environmental, and military molecules [13-14].

Characterization of Gold Nanoparticles

Various analytical techniques have been developed, in recent years, to characterize noble metal nanoparticles, according to their unique thermal, electrical, chemical, and optical properties, and to confirm their size, shape, distribution, surface morphology, surface charge, and surface area [28-29]. The common techniques of characterizing nanoparticles are as follows: UV–visible spectrophotometry, dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier transform infrared spectroscopy (FTIR), powder X-ray diffraction (XRD) and energy dispersive spectroscopy (EDS) [30-32]. Spectrophotometric absorption measurements in the wavelength ranges of 400–450 nm and 500–550 nm are used in characterizing the silver and gold nanoparticles, respectively [32-33].The morphology of AuNPscan now be(is) better characterized, due to recent developments in advanced microscopic techniques. These include SEM, TEM, HRTEM,and atomic force microscopy (AFM), which arecommonly(arecommonly)employed to determine and characterize their size,shape, and surface morphology [29,34]. SEM provides Nano scaleNanoscaleinformationaboutinformationaboutparticles and determines their surface morphology anddispersionanddispersion, while TEM is used to provide information aboutheaboutthenumber of material layers and broad evidence of uptakeand localization, composition, polymer tethering, and physicalpropertiesphysicalproperties[29]. Also, TEMis commonly used as a quantitative method to measure size,volume, and shape, and it produces mainly two-dimensional(2D) images of three-dimensional (3D) nanoparticles [35]. HR-TEM is used to determine the exact shape, size,and crystalline structure. AFM, which issimilarissimilarto the scanning probe microscopy, provides information about thesurface topography of AuNPs. AFM hasthehastheadvantage of obtaining 3D images in a liquid environment [29].

The dynamic light scattering (DLS) is used to characterize the surface charge and the size distribution of the particles suspended in a liquid. Electron microscopy is another commonly used method of characterization. Scanning electron microscopy and transmsissiontransmissionelectron microscopy are used for morphological characterization at the nanometer to micrometer scale. Theelemental composition of metal nanoparticles is commonly established using energy dispersive spectroscopy [33-36].

Synthetic route of Nanoparticles

Nowadays, there is a huge interest in the development of synthetic protocols in order to control thesize, shape, morphology, and crystallinity of metal nanoparticles. The methods for making nanoparticles can generally involve either a “top down” approach or a “bottom up” approach [33]. In top-down synthesis (Figure 3), nanoparticles are produced by size reduction from a suitable starting material. Size reduction is achieved by various physical and chemical treatments (Figure 1). Top down production methods introduce imperfections in the surface structure of the product and this is a major limitation because the surface chemistry and the other physical properties of nanoparticles are highly dependent on the surface structure [37].

In bottom up synthesis, the nanostructured building blocks of the nanoparticles are formed first and then assembled to produce the final particle [37]. The bottom up synthesis mostly relies on chemical and biological methods of production. The probable mechanism of nanoparticle synthesis by bottom up approach is shown in Figure 2. Of the biological methods of synthesis, the methods based on microorganisms have been widely reported [38-41]. Microbial synthesis is of course readily scalable, environmentally benign,and compatible with the use of the product for medical applications, but theproduction of microorganisms is often more expensive than the production of plant extracts.

Size control

There are several factors contributing to the final size of the AuNPs. The first is theretheirreductant used. Reductant plays the most important role oninthe nucleation process. Several synthetic methods with different reductants have been reported [15]. The Brust-Schiffrin method using NaBH4 as reductant can prepare AuNPs of 2-10 nm [15-16], the Turkevich method using citrate can prepare AuNPs of 10-20 nm,the Murphy method using ascorbic acid can prepare AuNPs of 10-50 nm [20], the Perrault method using hydroquinone can prepare AuNPs of 50-200 nm [21] and the polyol method using diols can prepare AuNPs in 20-200 nm range.The surface stabilizer is another critical factor to control the size and shape of AuNPs. The higher the concentration of the surface stabilizer, the finer, faster, and more completely coated AuNPs are formed, resulting in smaller size of the particles.Amole ratio between the reductant and gold ion also affects the particle size. Higher mole ratio between reductant and gold ion will produce morenucleimorenuclei, leading to smaller sizes [18-23].

Synthesis of Gold nanoparticles using plant extract

The properties of gold nanoparticles are very different from that of bulk, as the gold nanoparticles are wine red solution while the bulk gold is yellow solid. A tuber extract of *Dioscorea bulbifera* was used to produce gold and silver nanoparticles of various shapes Ghosh *et al.*, (2011). Production of spherical and triangular-shaped gold nanoparticles using fruit extract of Tanacetum vulgare have been reported Dubey *et al.*, (2010). Njagi *et al.*, (2011) used an aqueous extract of *Sorghum bran* to produce nanoparticles of iron and silver at room temperature. Kasthuri *et al.*, (2009) used a dilute phyllanthin containing extract derived from the plant *Phyllanthus amarus*, to produce hexagonal and triangular gold nanoparticles from $HAuCl_4$. Increasing the concentration of the extract led to the formation of spherical nanoparticles.Narayanan and Sakthivel (2008) produced gold nanoparticles using a leaf extract of *Coriandrum sativum* (coriander). The particles ranged in size from about 7 to 58 nm and had diverse shapes (spherical, triangular, decahedral). Raghunandan *et al.*, (2010) produced irregularly shaped gold nanoparticles using an extract of dried clove (*Syzygium aromaticum*) buds. The reduction and stabilization of gold nanoparticles were ascribed to the flavonoids present in the extract. Parida *et al.*, (2011) reported the synthesis of gold nanoparticles mediated by an extract of *Allium cepa*. The particles had an average size of 100 nm and could be internalized by MCF-7 breast cancer cells via endocytosis. In another method, Liu *et al.*, (2012) synthesized gold nanoparticles using extracts of Chrysanthemum and tea beverages. A nanoparticle-based assay was developed for quantifying the antioxidant properties of teas.Gold nanoparticles made using the extract were found to be superior to the extract as hypoglycemic agents in rats for the management of diabetes mellitus (Liu *et al.*, 2012). Daisy and Saipriya (2012) synthesized gold nanoparticles (55–98 nm) using an aqueous extract of *Cassia fistula.* Extracts of C. *fistula* bark are known to be hypoglycemic. Kumar *et al.*, (2012) used an aqueous extract of *Terminalia chebula* to produce gold nanoparticles with sizes ranging from 6 to 60 nm. These nanoparticles were active against both Gram-positive S. aureus and Gram-negative E. coli. In another Wu *et al.*, (2013) reported an approach for size and shape separation of NPs synthesized using *Cacumen platycladi* leaf extract. In the first step, size separation was performed via thedensity gradient centrifugation method. Then, the size-purified GNPs were subjected to agarose gel electrophoresis (AGE) to separate gold nanospheres from gold nanoplates. The authors observed that AGE cannot be effective in shape separation of nanoparticles without initial size separation by density gradient centrifugation. This report is one of the most important papers on sizeandsizeandshape purification of nanoparticles. In 2014, the extract of *Garcinia combogia* fruit was used for the production of GNPs in spherical and anisotropic shapes Rajan *et al.*, (2014).Huo *et al.*, (2018) used medicinal plants to synthesize AuNPs. Rootextracts of *Glycyrrhiza uralensis*have been extensively used asa traditional medicine for anti-viral, antioxidant, and anti-inflammatorypurposes due to the presence of glycyrrhizinand flavonoids.

The reaction of $HAuCl_4$ with Chineseliquorice extract occurred rapidly within 4 mins. Spherical AuNPs were obtained with a size of 12.25 nm.It was also found that that the red watermelon extract tended to produce sphere and hexagonal plates, while the green watermelon extract tended to generate triangular shaped nanoparticles. Both red and green watermelon extracts produced nanoparticles with similar antibacterial activity towardsboththowardsbothEshcherichia coli and Staphylococcus epidermidis. The gold nanoparticles were synthesized using the lichen *Parmelia sulcata* extract. The elemental composition and spherical shape of AuNPs were confirmed by energy dispersive spectroscopy and tranmissiontranmissionelectron microscopy. The average particles size is 54 nm. The potential effect of synthesized nanoparticles and lichen extract was evaluated for antioxidentantioxidantbioassays like DPPH and H_2O_2 and tested for mosquitocidal activity against *Anopheles stephensi*[27].

Table 1: DIFFERENT PLANTS SPECIES THAT HAVE BEEN USED FOR THE SYNTHESIS OF GOLD NANOPARTICLES

S. No.	Plant	Plant part	Shape	Size in nm	Reference
1.	*Azadirachta indica* A.Juss	Leaf	Spherical, triangle, hexagonal	50-35	[48]
2.	*Populous alba* L.	Leaf	Uniform	16.3 ± 0.7	[49]
3.	*Cicer arietinum* L.	Beans	Triangularprism	25	[50]
4.	*Alium cepa* L.	Leaf	Spherical and triangle	100	[51]
5.	*Macrotyloma uniflorum* (Lam)	Leaf	Flate and plate-like triangle	14-17	[52]
6.	*Justicia gendarussa* Bum.f.	Leaf	Spherical and triangle	20-42	[53]
7.	*Camellia sinensis* (L.) Kuntze	Leaf	Spherical	20-30	[54]
8.	*Pelargonium roseum* L.	Leaf	Hexagonal	2.5-27.5	[55]
9.	*Coriandrum sativum* L.	Leaf	Spherical triangle and a truncated	5-70	[56]

			triangle		
10.	*Mentha piperita*L.	Leaf	Nanoprism and spherical	90-150	[57]
11.	*Mirabilis jalapa* L.	Plant	Spherical and triangles	100	[58]
12.	*Rosa hybrid* L.	Petal	Triangles, pentagons, hexagonal and spherical	10	[59]
13.	*Mangifera indica* L.	Peel	Spherical	6.03-18	[60]
14.	*Gymnocladus assamicus* P.C. Kanjilal	Leaf	Hexagonal, pentagonal, triangular	4-22	[61]
15.	*Garcinia mangostana* L.	Peel	Spherical and hexagonal	32.96	[62]
16.	*Pogestemon benghalensis* (Burm. F.) O. Kuntze	Leaf	Cubic	13.07	[63]
17.	*Vitis vinifera* L.	Fruit	Spherical	5-40	[64]
18.	*Nerium oleander* L.	Leaf	Spherical	2-10	[65]
19.	*Butea monosperma* (Lam.) Taub.	Leaf	Spherical	10-100	[66]
20.	*Arachis hypogaea* L.	Leaf	Spherical	110-130	[67]
21.	*Nyctanthes arbortristis* L.	Flower	Spherical, triangular	19.8	[68]
22.	*Hibiscus cannabinus* L.	Leaf	Spherical	10-13	[69]
23.	*Sesbania grandiflora* (L.) Poiert	Leaf	Spherical	7-34	[70]
24.	*Salix alba* L.	Leaf	……	50-80	[71]
25.	*Eucommia ulmoides* Oliv.	Leaf	Spherical	…..	[72]
26.	*Galaxaura elongate* J. Agardh	Leaf	Spherical	3.85-77.13	[73]
27.	*Ocimum sanctum* L.	Leaf	Hexagonal	30	[74]
28.	*Torreya nucifera* (L.) Siebold and Zucc.	Leaf	Spherical	10-125	[75]
29.	*Olea europaea* L.	Leaf	Triangular, hexagonal, Spherical	50-100	[76]

30.	*Rosa indica* L.	Leaf	Spherical	23.52-60.83	[77]
31.	*Pistacia integerrima* J.L.Stewart ex Brandis	Leaf	……	20-200	[78]
32.	*Terminalia arjuna* (Roxb.) Wight & Arn.	Leaf	Spherical	60	[79]
33.	*Euphorbia hirta* L.	Leaf	Spherical	6-71	[80]
34.	*Morinda citrifolia* L.	Leaf	Spherical	12.17-38.26	[81]
35.	*Ziziphus mouritana* Lam.	Leaf	Spherical	20-40	[82]
36.	*Aloe vera* (L.) Burm.f.	Leaf	Spherical	50-30	[83]
37.	*Anacardium occidentale* L.	Leaf	Spherical	6	[84]
38.	*Chenopodium album* L.	Leaf	…….	12-10	[85]
39.	*Dioscorea bulbifera* L.	Tuber	Spherical	13	[86]
40.	*Pelargonium graveolens*L'Hér.	Leaf; Stem	Spherical; Spherical	16-40; 8-24	[87], [109]
41.	*Mucuna pruriens* (L.) DC.	Leaf	Spherical	6.17-7	[88]
42.	*Parthenium hysterophorus* L.	Leaf	Face center cube	50	[89]
43.	*Psidium guajava* L.	Leaf	Spherical	20-30	[90]
44.	*Cacumen platycladi* L.	Leaf	------	Variable	[91]
45.	*Rosa rugosa* Thunb.	Leaf	Hexagonal	12	[92]
46.	*Tanacetum vulgare* L.	Leaf	Spherical and triangular	16	[93]

47.	*Terminalia catappa* L.	Leaf	Spherical	10-30	[94]
48.	*Nigella arvensis* L.	Leaf	Spherical	3-37	[95]
49.	*Scutellaria barbata* D.Don	Leaf	Spherical	154	[96]
50.	*Gnidia glauca* L.	Flower	Spherical	10	[97]
51.	*Cinnamomum japonicum* Sieb.	Leaves	Spherical	10-50	[98]
52.	*Salicornia brachiata*L.	Leaf	Spherical	22-35	[99]
53.	*Cicer arietinum* L.	Beans	Triangular	191	[100]
54.	*Terminalia chebula* L.	Fruit	Spherical	60	[101]
55.	*Trichoderma koningii*	Leaves	Triangular	30-40	[102]
56.	*Tamarindus indica* L.	Flower	Triangular	2-40	[103]
57.	*Pyrus sp.*L.(Pear)	Fruit	Triangular, hexagonal	200-500	[104]
58.	*Magnolia kobus* DC. and *Diopyros kaki* Thunb.	Leaf	Triangle, pentagons and hexagons	5-300	[105]
59.	*Medicago sativa* L.	Plant extract	Irregular, tetrahedral, hexagonal platelet, decahedral, icosahedral	2-40	[106]
60.	*Emblicaofficinales* L.	Fruit	Triangular	15-25	[107]
61.	*Cymbopogon citrates* (DC.) Stap.	Leaf	Triangular and spherical	10-30	[108]
62.	*Pelargonium graveolens* L'Hér.	Stem	Spherical	8.3-23.8	[109]

63.	*Eucalyptus camaldulensis* Dehnh.	Leaf	Triangle and hexagonal	1.25-17.5	[110]

Advantage of Biosynthesis

SynthesismethodSynthesismethodis simple and facile. It is easy to control the size and shape of theNPs by altering the reaction parameters and the reduction of NPs is relatively rapid and cost effective.

Disadvantage of Biosynthesis

It is difficult to determine the reactive components in plants because plant extracts contain many organic compounds.

Biological evaluation of gold nanoparticles

Presently, metal nanoparticles are of much importance because of their catalytic activity, optical properties, electronic properties, antimicrobial activity,and magnetic activity (Duran, Marcarto, De Souza, Alves & Esposito, 2007; Kowshik *et al.*, 2003). In medicine, nanomaterials have been used in specific applications such as tissue-engineered scaffolds and devices, drug delivery systems, cancer therapy,and bioanalytical diagnostics and therapeutics (Namasivayam, Gnanendra, & Reepika, 2010; Mukherjee *et al.*, 2015; Vlerken & Amiji, 2006).

NPs contain small atoms or molecules that possess unique properties which vary from their bulk counterparts. Hence, they perform differently in terms of electronic, magnetic, optical, physical, and chemical properties [89].Spherical AuNPs play an important role forin the future of bio-nanotechnology development. They have large surface-to-volume ratios, good optoelectronic properties, excellent biocompatibility, and low toxicity. AuNPs tend to interact with biomolecules (such as lipid, nucleic acid and proteins) due to their multiple surface compatibility properties. The immediate adsorption of biomolecules to AuNPs is called the “nanoparticle-protein corona”. This interaction provides greater promise for clinical use. The effect of such a corona reduced the release of paclitaxel from Nano carriers and this effect is dependent on protein concentrations [90].

AuNPs have been shown to be non-toxic to normal L-cells when used at different amounts (from 1 to 100µL) [91].Another toxicity test was completed by Irama using radish. The root length and percent of seed germination waswheredetermined. Their research showed that AuNPs of sizes greater than 30 nm rarely entered the cell nucleus; hence, they may be more suitable for drug delivery [92]. The toxicity of AuNPs was determined using in vivo animal models where it was found that toxicity was size dependent. Particles that were 10 nm in size were present in almost every tissue while larger particles were only detected in the liver, blood, and spleen [93]. Based on the work from Sadauskas *et al.*, it was found that AuNPs gradually decreased and were removed from the circulation system to one fifth of their original amount after 6 months mainly by Kupffer cells. It was a long-term process. [94,102]. However, the damage caused by AuNPs was not permanent as cells were able to recover following AuNP removal. Near full recovery occurred for the cells after 14 days of AuNP removal (13nm and 45 nm in diameter). The number of vacuoles decreased which in turn allowed the cells to form normal actin fibers and increase their production as the cells divided and the concentration of AuNPs decreased [95]. Still, more work is needed before AuNPs can be widely used clinically as current studies, especially involving humans, remain fragmented.

Govindaraju *et al.*,(2020) reported antimicrobial and anticancer activity of synthesized nanoparticles using *Pongamia pinnata* leaf extract. SynthesizedgoldSynthesizedgoldnanoparticles inhibited breast cancer cell line (MCF-7) proliferations with an efficiency of IC50 of 1.85ug/mL.

Antimicrobial activity

AuNPs are also capable of fighting bacteria, fungi, and other pathogens [96-97]. AuNPs exhibit antibacterial effects when they attach to the surface of a microbial cell wall because of their surface charge. The physicochemical surface modification between bacteria and NPs will release reactive oxygen species (ROS). This will cause protein denaturation, DNA destruction, mitochondrial dysfunction, and finally cell death. [98]. antifungal activity of AuNPs may be due to binding of the NPs on the microbial surfaces through electrostatic interactions too. This reaction will inhibit the growth of fungi and generate ROS. The NPs will interrupt cell membrane permeability by attaching and collapsing intercellular communication.The synthesized Au NPs have shown enhanced antibacterial activity. It is very interesting that all these green synthesized Au NPs show efficient antibacterial activity against certain bacterial strains, especially compared to chemically synthesized Au NPs which showed nearly no antimicrobial activity against similar strains. The antibacterial activity may be due to the synergistic effect of the combination of Au NPs and extracts. Antimicrobial potential of the NPs areisaffected by the size and surface chemistry.

Anincrease in size will decrease their activity and vice versa. WhichThisis also supported by study of Ahmad according to their study 7 nm Au NPs restrict the trans membrane H^+ efflux of the Candida species more than the 15 nm Au NPs. Moreover, despite the size, the antimicrobial activity was also different in the case of cell wall composition. Au NPs showed thehighest activity against gram negative bacteria than gram-positive bacteria (Figure 4). The Antimicrobial property of nanoparticles against Staphylococcus aureus, Pseudomonas aeruginosa, and E.coli has been investigated [99]. Nanoparticles were found to be cytotoxic to E.coli. The fluorescent bacteria were used to investigate the antimicrobial properties of nanoparticles. Recently studies have demonstrated that specially formulated metal oxide nanoparticles have good antimicrobial activity. Its compounds havehadstrong inhibitory and bactericidal effects as well as a broad spectrum of antimicrobial activities of fungi, viruses, and bacteria since ancient times [100]. Due to the development of resistant strains resistance of bacteria to bactericides and antibiotics has increased [101]. Some antimicrobial agents are extremely toxic and there are a vital needs and much interest in finding ways to formulate a new type of safe and cost-effective biocidal material [102].

AuNPs show excellent antibacterial activity against E. coli by absorbing light and converting it into heat. The growing drug resistance of fungal strainsalso demands the development of new drugs for thebetter treatmentoftreatmentoffungal diseases [128-32]. Among the various nanoparticles, AuNPs aresensitivearesensitiveto candida cells, which can inhibit the growth andkill the fungal pathogen C. *albicans*. They increase the ROS and damage the cellmembranecellmembraneby their unique properties, which include convertinlightconverting lightto heat when irradiated and strong anionic binding with thefungal plasma membrane [143-144].

The general consensus is that AuNP drug conjugates exhibit greater antibacterial activity than individual nanoparticles and drugs. Payne *et al.*, (2016) evaluated the antibacterial activities of kanamycin and AuNPs–kanamycin conjugates against the Gram-positive Staphylococcus epidermidis and the Gram-negative Enterobacteraerogenes,Enterobacteraerogenesand concluded that the minimum inhibitory concentration of the conjugate was significantly lower than that of free kanamycin. Similar conclusions were drawn by Rattanata *et al.*, (2016), who evaluated the activities of gallic acid and AuNP–gallic acid against the foodborne pathogenic bacterial species *Plesiomonasshigelloides* and *Shigellaflexneri B.* Furthermore, analysis of the underlying mechanism by Fourier transform infrared spectroscopy revealed that AuNP–gallic acid altered lipids, proteins, and nucleic acids of the bacterial cell membrane [154]. Bagga *et al.*,(2017) indicated that 27·2-nm AuNP–levofloxacin conjugates were more efficient than levofloxacin alone, and improved the antibacterial efficacy against Staphylococcus aureus, Escherichia coli, and Pseudomonas

aeruginosa by 1·94, 2·89 and 1·46 times respectively.Peng *et al.,* (2016) demonstrated that an AuNPs antimicrobial peptide system had greater antimicrobial efficacy than free antimicrobial peptides in rat mesenchymal stem cells, and they attributed the improvement to the high peptide density on the AuNP surface.It has been speculated that AuNPs interact with bacterial components, such as lysosomes, ribosomes, and enzymes, and change the permeability of the cell membrane, leading to the disruption of the electrolyte balance, enzyme inhibition, and protein deactivation (Yang *et al.,* 2009).

Payne *et al.,* (2016) evaluated the antibacterial activities of kanamycin and AuNP–kanamycin conjugates against the Gram positive Staphylococcus epidermidis and the Gram negative Enterobacter aerogenes and concluded that the minimum inhibitory concentration of the conjugate was significantly lower than that of free kanamycin. Rattanata *et al*., (2016) evaluated the activities of gallic acid and AgNPs gallic acid against the food borne pathogenic bacteria species Plesiomonas shigelloides and Shigella flexneriB. Furthermore, analysis of the underlying mechanism by Fourier transform infrared spectroscopy revealed that AuNPs gallic acid altered lipids, proteins and nucleic acids of the bacterial cell membrane. In depth, research has identified various mechanisms by which AuNPs drug conjugates enter and influence micro-organisms. Small angle X ray scattering analyses have indicated that AuNPs conjugates adhere to and penetrate the bacterial cell wall, resulting in the disruption of the cellular environment and leading to cell lysis due to the leakage of cellular components (Payne *et al.*,2016). A similar mechanism was observed for AuNPs gallic acid conjugates, which disrupted the cell membrane structure and integrity (Rattanata *et al.*,2016) and (Rajanetal.,2017) reported that the antibacterial tests were performed using the agar well diffusion with selected gram-positive (*S. aureus, P. aeruginosa*) and gramnegativebacteria(*Bacillus* sp. and *E. coli*).

Anticancer activity of gold nanoprticles

The International Agency for Research on Cancer estimates of the incidence of mortality and prevalence from major types of cancer, at thenational level, for 184 countries of the world revealed that there were 14.1 million new cancer cases, 8.2 million cancer deaths, and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide. By2030, it is projected that there will be 26 million new cancer cases and 17 million cancer deaths per year.Today, despite considerable efforts, cancer still remains an aggressive killer worldwide. Moreover, during the last decade, novel synthetic chemotherapeutic agents currently in use clinically have not succeeded in fulfilling expectations despite the considerable cost of their development. Therefore, there is a constant demand to develop new, effective, and affordable anticancer drugs. From the dawn of

ancient medicine, chemical compounds derived from plants have been used to treat human diseases. Natural products have received increasing attention over the past 30 years for their potential as anovel cancer preventive and therapeutic agents.Gold nanoparticles have been investigated in diverse areas such as in vitro assays, in vitro and in vivo imaging, cancer therapy, and drug delivery. In order to be useful for cancer treatment, the AuNPs must be noncytotoxic (i.e. nontoxic for cells) for normal cells. This biocompatibility of gold nanoparticles helps to high utilization in thebiomedical field.

AuNPs can be employed as a drug for cancer treatment. The small size of NPs enables them to penetrate through cancer cells for targeted treatment. The presence of large vascular pores on the vessels that supply oxygen and nutrients to the tumor sites and inflamed tissues enables NPs to pass through easily and accumulate at these areas. [103].Many researchers have shown that AuNPs have the ability to combat cancer cells successfully (Figure 5). AuNPs synthesized using Gymnema sylvestre, or commonly known as cowplant, exhibited cytotoxic effects towards Hep2 cells. Morphological changes were observed in Hep2 cells after treatment with AuNPs. Increases in the level of reactive oxygen species and nucleus changes were determined and suggested that the death of Hep2 cells was mediated by apoptosis [104]. Another cervical cancer cell, HeLa cell line, reacted towards AuNPs as well. Morphological changes such as rounding, shrinking and granulation were observed. The activity of AuNPs was due to easy penetration of the NPs through the cell membrane [105]. AuNPs have also reacted on other tumor cells, Ehrlich's Ascites Carcinoma, breast cancer cells and MCF-7 cells to name a few. Green tea polyphenols have been utilized to synthesize AuNPs. A comparison was made between green tea synthesized AuNPs and EGCG synthesized AuNPs. Both NPs were able to induce apoptosis in tumor cells while protecting normal hepatocytes from tumor cell damage. However, green synthesized AuNPs showed enhanced tumoricidal and hepatoprotective properties [106]. AuNPs that were synthesisedsynthesizedby Actinidia deliciosa showed 71% viability at their highest concentration (350µg/mL) when tested on HCT-116 cells using an MTT assay. The NPs exhibited a cytotoxic effect in a concentration dependent manner [107].

Zharov *et al.,* (2005) showed that the absorbance wavelength (in the visible range) of small gold nanospheres is not optimal for in vivo applications, besides investigating the assembly of gold nanoclusters on the cell membrane. Chithrani*et al.,* (2007) research shows the effect of AuNPs size on Hela cells due to internalization time. The internalization time of AuNPs measuring between 14 and 74 nm is independent of their size. However, this difference modifies the number of internalized particles. They also revealsrevealthat the accumulation ofAuNPs near cancer cells is because of the Enhanced Permeability and Retention (EPR) effect and the vectorization is called a ''passive'' one. Dhar *et al.*, (2011) has reported the cellular uptake studies and cytotoxic effect of biosynthesized gold nanoparticles human glioma cell line LN-229 and human glioma stem cell line HNGC-2. The

gold nanoparticles showed greater cytoxicity by killing the glioma cell lines andthe glioma stem cell lines also. Lokina and Narayanan (2013) studies showsshowthat cytotoxicity on Hela cancer cell of gold nanoparticles synthesized from grape fruitgrapefruitextract was very inevitable results withinaddition to antimicrobial activity.

Divakaran *et al.*, (2019) reported that AuNPs are more significant in the research field owing to their non-toxic effects; self-assembled natural, and improved drug delivery [129].*Scutellaria barbata* has a potent antitumor activity in breast cancer [130], colorectal cancer [131], hepatocarcinoma [132], skin cancer [133], lung cancer [134] and ovarian cancer [135]. Moreover, Lee *et al.*, (2017) reported that the active fractions of *Scutellaria barbata* have anti-inflammatory activity in BV-2 cells. [136]. The Main properties of nanoparticles to be an effective drug delivery agent includesincludemonodispersity lack of cytotoxicity and simple mechanism of interaction with desired ligands [155]. Based on these characteristics many nanoparticles have been synthesized and used in cancer treatment, drug delivery systems and imaging such as dendrimers, quantum dots, polymer gels, gold nanoparticles [118-22].

Recent progress in inorganic material based nanoparticles for cancer therapy and imaging, mutiplemultiplenano vehicle have been developed and evaluated. Zahra *et al.*,(2019) studied that nanocomposite of zinc oxide and gold nanoparticles was used as a platform for immobilizing thiolated TB DNA (Probe DNA) a simple and cost effective electrochemical DNA biosensor was developed. Abdel-Ghany*et al.*, (2020) effect of gold nanoparticlesnanoparticleson induce G2/M cell cycle arrest and enhance the expression of E- cadherin in breast cancer cells MCF-7.Govindaraju *et al.*,(2020) reported antimicrobial and anticancer activity of synthesized nanoparticles using pongammia pinnata leaf extract. Synthesized gold nanoparticles inhibited breast cancer cell line (MCF-7) proliferaction with an efficiency of IC_{50} of (1.85 µg/mL).In vitro anticancer evaluation against HepG2 cell lines was conducted by MTT assay for craton spassiflorus extract derived AuNPs in different conc. 5 to 150 µg/mL studied.

Conclusion

The biological application of MNps have(has)increased the need to develop aplant-based method in the synthesis of these NPs. Plants are inexpensive, available and renewable source. Also, it is very simple to prepare an extract from plants. The great variety of plants in nature leads to great diversity in type and amount of capping and reducing agents from plant extract which make possible the synthesis of MNps of different shapes and morphologies. Further, there isevidenceisevidencethat nanoparticles exhibit an array of genotoxic effects in ahigher organism. This raisesconcern about possible impacts to higher organism including humans. Although significant progresshas been made

to the mechanisms of nanoparticles toxicity, further research is required to fullyunderstandfullyunderstandthe processes involved and to safely exploit the tremendous antimicrobial propertiesnanoparticlesproperties of nanoparticleswithout jeopardizing human health, critical infrastructure, and the environment. Futurein-vitro, in-vivo, and environmental studies should consider more systematically the various effects ofaquatic ofaquaticchemistry on nanomaterial fate and toxicity. The products of nanoparticles have a large surface area to volume ratio, which is their most important feature responsible for the widespread use of nanomaterial's in mechanics, optics, electronics, biotechnology, microbiology, environmental remediation, medicine, numerous engineering fields, and material science.

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FIGURE LIGENDS

Figure1: Faraday's gold nanoparticle dispersion (left), TEM image from this nanoparticles (middle) and Faraday's portrait (right) [91].

Figure 2: Different shape of gold nanoparticles [152].

Figure 3: Scheme of synthesis of nanoparticles

Figure 4: Schematic diagram for antibacterial activity of Au nanoparticles [154].

Figure 5: Mechanisms of anticancer activity for AuNPs [155].

Figure1: Faraday's gold nanoparticle dispersion (left), TEM image from this nanoparticles (middle) and Faraday's portrait (right) [91].

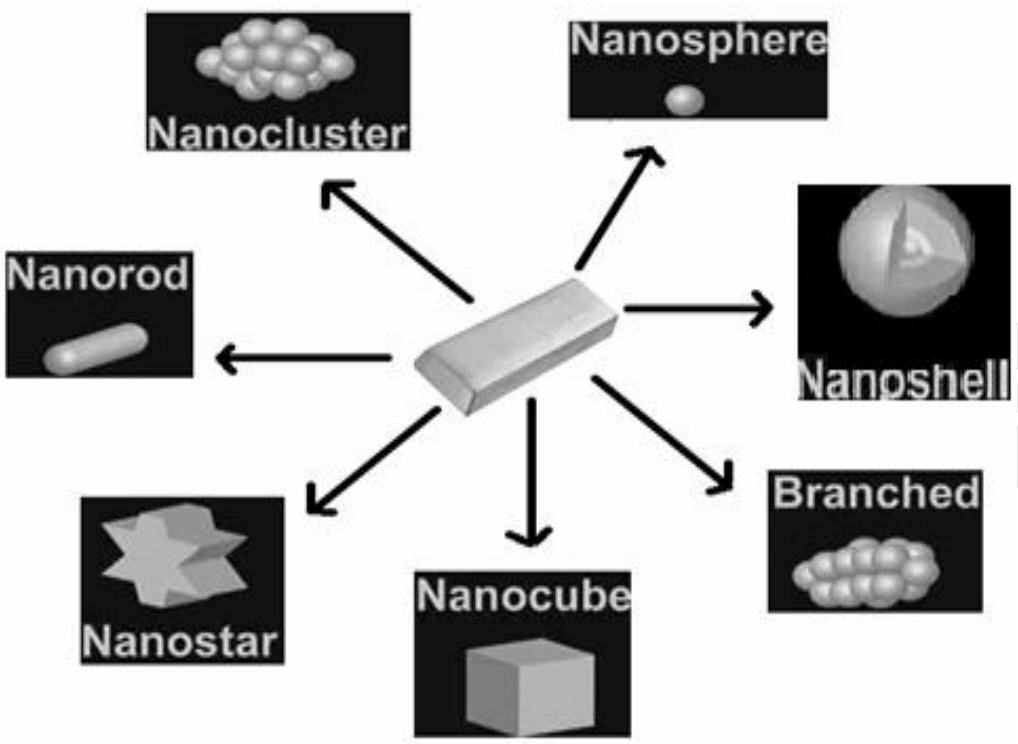

Figure 2: Different shape of gold nanoparticles [152].

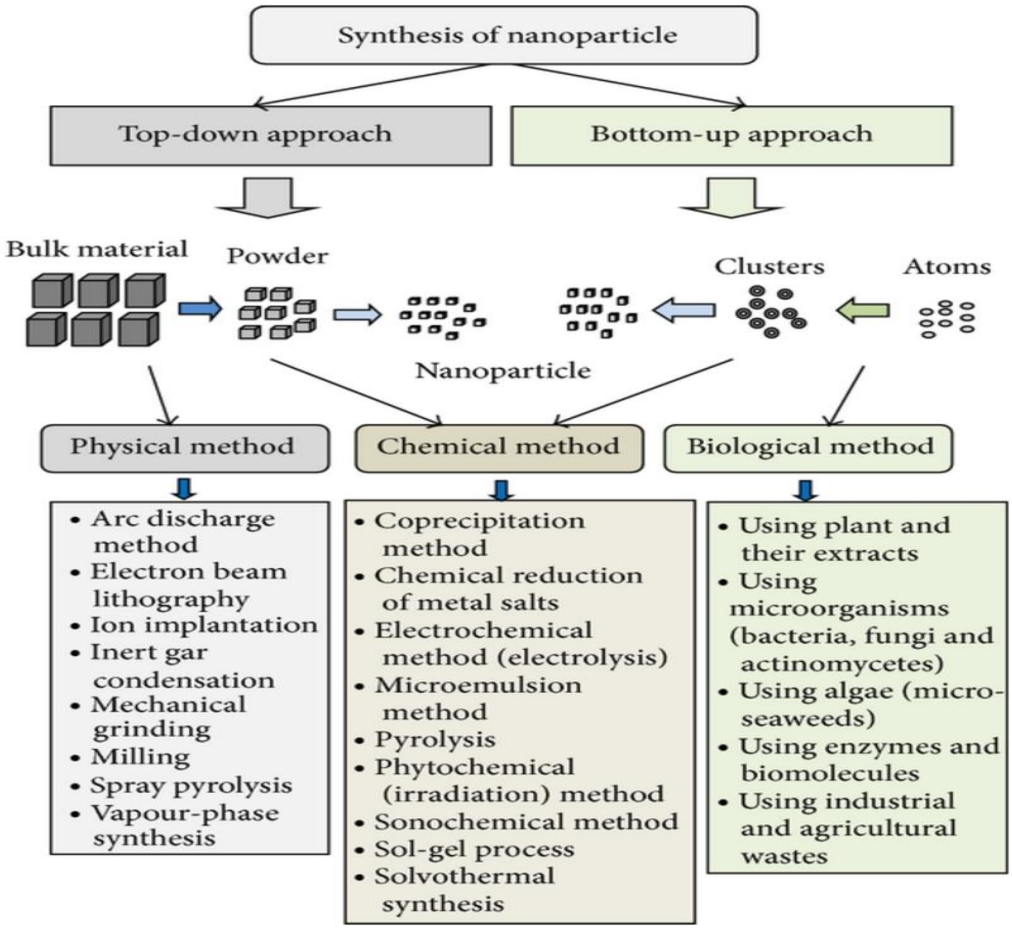

Figure 3: Scheme of synthesis of nanoparticles

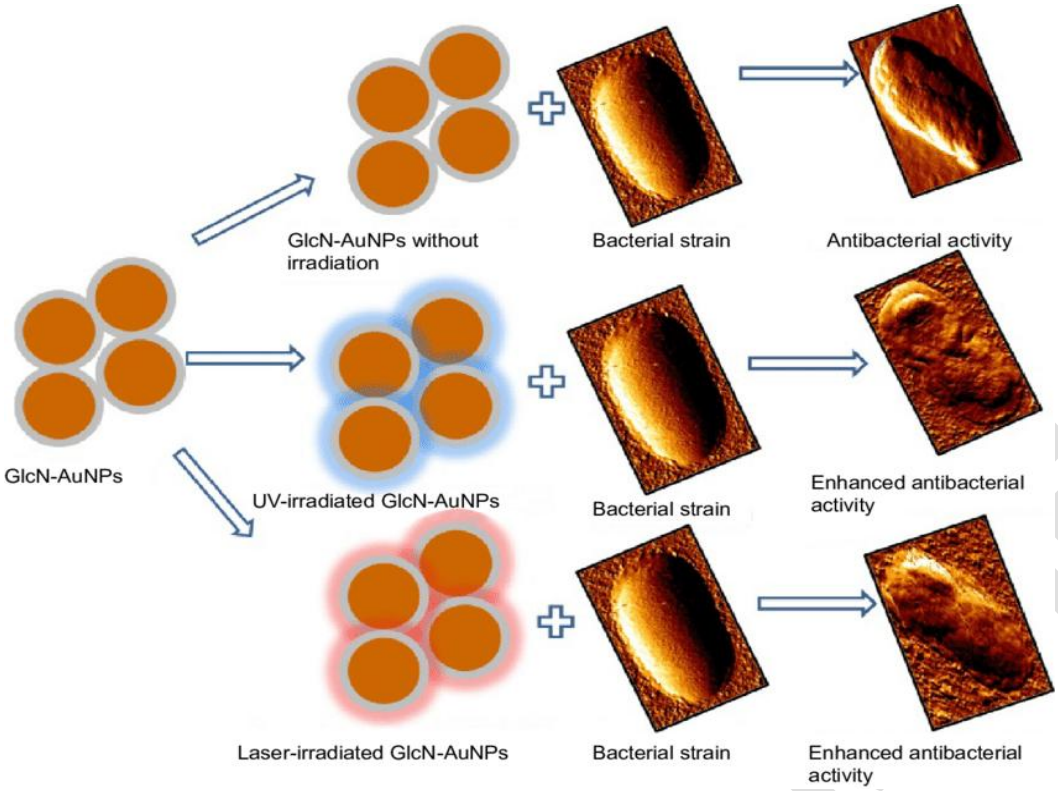

Figure 4: Schematic diagram for antibacterial activity of Au nanoparticles [154].

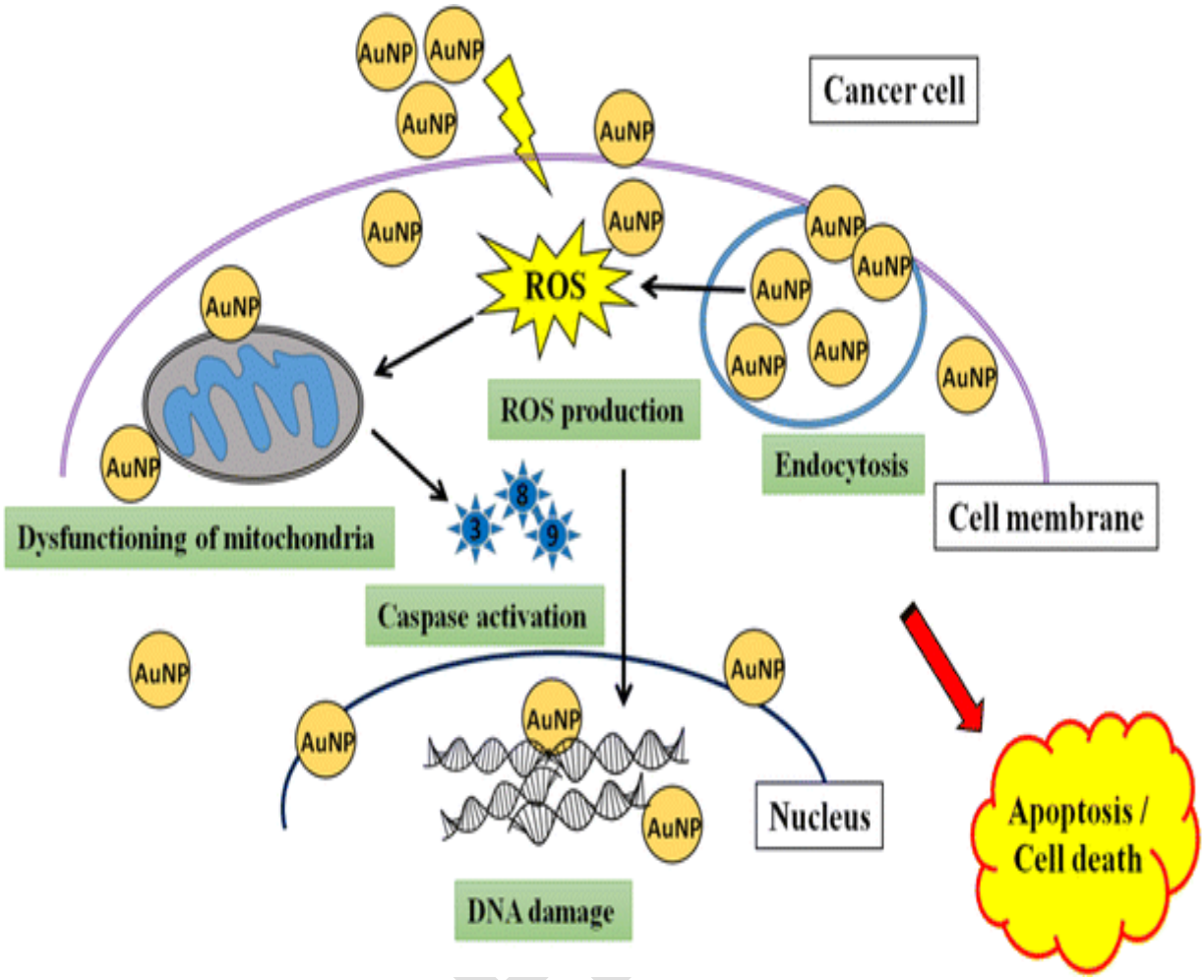

Figure 5: Mechanisms of anticancer activity for AuNPs [155].