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The utilization of plant extracts/biomaterials for the green synthesis of nanoparticles, their biological activity and mode of action

Ali Esmail Al-Snafi [1], Hussein Ali Hussein Al-Sa'idy [2, *] and Hussein Kamil Hamid [3]

[1] Department of Pharmacology, College of Medicine, University of Thi-Qar, 64001, Iraq.
[2] Department of Environment and Pollution, Marshes research center, University of Thi-Qar, 64001, Iraq.
[3] College of Pharmacy, National University of Science and Technology, Thi-Qar, 64001, Iraq.

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Abstract

Nanotechnology is one of the modern approaches that has found access to the medicinal as well as pharmaceutical uses where the nanoparticles of the nobel as well as other metals nanoparticles and their oxides have been reported to exploite various biological activities particularly antimicrobial besides antineoplastic activities. In addition, metal/metal oxides nanoparticles have also been proposed to have diagnostic applications in radioscanning of neoplastic diseases besides pharmaceutical application in neoplastic drugs delivery. Green/eco-friendly synthesis of these nanoparticles using biomaterials is considered as an innovatory approach for their production through which attaining economically beneficial along with drastic polluting methods avoidance advantages. In this context, plants extracts are increasingly finding the way for their production. In this survey, the green chemical synthesis approaches of nanoparticals of different metals and their oxides, their medical uses and biological activities, particularly antimicrobial mechanism of silver nanoparticles, as well as antineoplastic activity are discussed. The outcomes of this survey encourage us to conclude the feasibility of investment in the investigations in this approach.

Keywords: Plant; Extracts; Biomaterials; Green; Nanoparticles; Biological activity

1. Introduction

Nanotechnology is an approach involve the synthesis of wide spectrum nano-size materials of various shapes commonly known as nanoparticles that ranges from 1 to 100 nm diameter [1, 2]. This approach has leads the wayfor investigation of novel scientific applications of various uses [3]. Nobel metals such as gold and silver have got a considerable investigators interest for their multiple benefits reported in the fields of biosciences [4]. Interestingly, nanotechnology has emerged as a novel approach for various human disease treatment particularly cancer establishing a new branch of medicine called nanomedicine as it is involved in the fields of disease diagnosis and treatment besides the drug delivery as well as biocompatible material synthesis. Materials in nanoscale are of enhanced biological activity as well as the drug pharmacokinetics, of lower required effective concentration, and of synergistic activity to the conventional drugs [5]. Silver, platinum and gold nanoparticulates have been through investigated for various medicinal uses and finds their way for the development of novel diagnostic and treatment approaches for various diseases [6] including cancer [7] in addition to the development of biosensors [8] and cells labeling [9]. silver nanoparticulate are most widely investigated and used in medicinal and biological fields [10, 11], however, in this context silver, goldium and other magnetic nanoparticles have been found penetrate the blood brain barrier more easily in mouse brain model [12-14]. Nevertheless, within the last decade ultrasound method has been used for synthesis in nanotechnology approach [15, 16].

*Corresponding author: Hussein Ali Hussein Al-Sa'idy
Department of Environment and Pollution, Marshes research center, University of Thi-Qar, 64001, Iraq.

Currently, because of their innovatory interesting implications of nano-materials they have attained a special attention by the researchers [17]. In general, nano-particles are solids of very tiny sizes that ranges from 10 to 1000 nm diameter of an extraordinary large surface area, stable shapes, elevated surface energy, zeta potential, and physicochemical properties as compared to micro-size particles leading to expanding their implications in the innovatory developing technologies and uses [18, 19], since, they exhibit atom like behaviors particularly those with particle size less than 100 nm [20]. Nano-particles of sizes of 10-100 nm size have characteristic properties to be useful for biological, medicinal and pharmaceuticals fields that have gained interests of many investigators and development researchers [21-23]. Remarkably, metals as well as metal oxides have various physical characteristics including catalytic, optical, elevated surface energy and magnetic properties besides other physicochemical properties contributing to their extraordinary biological properties explaining their implications in the fields of chemistry, medicine, biotechnology, particularly gold nanoparticles, as well as various fields of physics [23, 24]. Thus, they have find their ways to be used in medicine as antimicrobial agents [25], diagnostic agents (imaging and sensing), cell labeling, delivering of drugs, anticancers, tissue engineering, artificial implants [26-28] wound dressings, antibacterial formulations, surgical instruments and bond prostheses particularly nanoparticles of Platinum (Pt), Gold (Au), Silver (Ag) and Palladium (Pd) [29, 30]. Consequently, a new field of medicine have been recently introduced known as nanomedicine at least to enhance the medicinal therapy of diseases [7] as well as other biomedical applications [31].

Moreover, as drug delivery tool nanoparticulates are investigated for their brain drug targeting hence enhancing drugs efficacy along with declining its side effects. This approach of investigation is attributed to their characteristic large surface to mass ratio, quantum properties along with their drugs, proteins and probes loading capacity particularly those modified with polymers as they can penetrate the blood brain barrier besides prolonged sustained drug with protection against metabolic drug inactivation advantages [32]. Furthermore, nanoparticules are found to maintain sustained anticancer drugs release [33, 34], cancer tissues targeting, cancer cells penetration and capability to transport a broad spectrum of antitumor agents particularly via polymers encapsulation approach [35, 36]. Consequently, nanoparticulates of gold, silver, copper, titanium dioxide, cerium dioxide and iron oxide have the capability if chemotherapeutic anticancer drugs delivery [37-39]. Meanwhile, it is found that the nano-particulates size of optimum cells internalization capacity is 100-400 nm which can evade the reticuloendothelial system macrophages uptake or escape outside the cells [40]. Various methods of surface modification is used to enhance the brain nanoparticulate dependent drug delivery including the use of surfactants including polysorbates [41, 42] such as polysorbate 80 that behaves in a low density lipoprotein mimic blood brain barrier penetrating capability through binding to the LDL receptor toping their endothelial cells [43-45]. Biomolecules like polysaccharides and plant extracts coated gold, silver and zinc oxide nanoparticles are reported to be effective for wound healing via provoking of apoptosis, angiogenesis, re-epithelialization, tissue necrosis, scar formation, bacterial clearance and reduce cytokines (IL-6 and IL-10) [46-49]. Therefore, a combination of physiologically important metals nanoparticulates (zinc and coppers) and the therapeutic plants to give rise an efficiently effective implications [50]. However, their biological, medicinal as well as their pharmaceutical uses are determined by their potential toxicities besides their biocompatibilities, hence, biologically green approaches of synthesis are recently preferred as they tremendously decline their toxicities along with inclining their biocompatibility [23]. In this context, nanoparticulates exhibit genotoxicity through an indirect mechanisms via either interaction with the DNA or via reactive oxygen species formation explained by their rapid passage across the cell compartments to the DNA and cells organelles through their small sizes as well as surface reactivity [51, 52]. Other example is the eco-friendly produced silver nanoparticulates to improve drug efficacy along with reducing its adverse effects [7].

2. Green bioorganic synthesis of nanoparticles

Green synthesis of nanoparticles have become an attractive approach using ecofriendly as well as non-toxic materials, despite the availability of several other physical and chemical methods. In this field of nanotechnology, natural sources of living beings are used in eco-friendly methods for nanoparticles use [53-58]. Several green methods have been reported for green synthesis of nanoparticulates for medicinal use [59-61], yet, all of them belong to two general approaches. The firsts is the top-down approach that involve breaking down larger fragments into smaller nano-size ones via adapting techniques involve grinding, ablation and cutting while the second bottom-top approach invests the chemical properties of atoms and molecules to attract each other then agglomerate into larger nano-size structure via using sol-gel, chemical vapor deposition, Pechini, microemulsion, green synthesis reduction methods…etc. [62]. In case of green biosynthesis of nanoparticles naturally occurring chemicals are used as reluctant as well as capping agents obtained from plant extracts, microorganisms (bacteria and fungi) and alge...etc [62-64], hence making use of their multiple advantages including low coast, toxicity, environment contamination and harshness of synthesis conditions besides their relatively high safety, larger production quantities, sustainable, higher aqueous solubility if prepared in water and better defined size/morphology [62, 64-71].

In this context, biomolecules such as fatty acids, polysaccharides, proteins, plants phytochemicals/secondary metabolites serves as bio-reductants as well as capping agents for metal and metal oxides nanoparticals biosynthesis [72-74]. Plants phytochemicals including phenolic compounds are the most widely used bio-reductants in this approach for the same formerly mentioned advantages [75], besides, being even faster bio-reductants than micro-organism produced biomolecules [62, 63, 76-79] as they are powerful antioxidant compounds [80]. Different plant parts extracts are involved in the biosynthesis of nanoparticles including that of the roots, flowers, seeds and stems, however, leaves extracts are the richest source of bio-reductants besides being capping, complexing, polymerizing and stabilizing agents [64, 74, 81-87] thus, they are considered as an excellent replacement to the chemically harsh reductants like sodium borohydride as well as physical methods of various limitations and drawbacks for the synthesis of medicinally useful gold, silver and gold-silver-copper alloy nanoparticles [88-94]. Various plants phytochemicals are involved in the nanoparticles eco-friendly synthesis including amino acids, alkaloids, other amine compounds, phenolics, bioactive polyphenols such as flavonoids, citric acid, terpenoids,enzymes, vitamins, proteins, lipids, sugars, polysaccharides, sapogenins, tannins, terpenoids, polyols, pigements and other organic compounds such as alcohols and aldehydes that acts as powerful reducing, chelating, capping, stabilizing, agents that besides reducing the metals ions, they stabilized the nanoparticle surface hence preventing their agglomerization [74, 78, 81, 95-105]. The most famous bio-reduction and capping agents involved in nanoparticles biosynthesis are polyphenolics due to their antioxidant activity as well as easiness of nanoparticles surface absorbance [59, 61, 62, 106-109].

However, the metal ions/salts reduction capacity of the plant extracts is well known since 1900s although the exact reducing agents involved in the nanoparticles synthesis have been discovered later within the last three decades where plants tissues/extracts are used for the simplicity of the method [60, 78, 103, 110]. In addition, the type of the extract, phytochemicals constituents and their concentration besides, the reaction pH, solvent used, and volume are fundamentally affect the nanoparticles bio-synthesis process [12, 74,111, 112], therefore the greater the availability of plants secondary metabolites within the reaction medium the more rapid the nanoparticles production [113]. Nevertheless, the quantity of the reaction mixture as well as the metal/metal oxide chemical source to the extract ratio are also other nanoparticles bio-synthesis rate significantly influencing factors as well as affecting their morphology and biological characteristics [114, 115].

Some have reported that iron metal source to *Azardirachta indica* extract ratio of 1:21 has resulted in 98-200 nm size range iron nanoparticles ranging between 200 to 600 nm which has more agglomerates however, its antibacterial activity enhanced as the ratio of mixing is altered from 1:2 to 1:5. Furthermore, variation of the plant extract intervene with the particle size, shape as well as their physicochemical characteristics, hence their biological activities depending on the capping, reducing, chelating and stabilizing phytochemical [23, 74, 115-117], hence through which at least nanoparticle size and morphology are controlled [118]. Therefore, in order to optimize the synthesis method at least the metal precursors as well as reducing/stabilizing agent (extract) quantities in addition to the reaction temperature and pH are carefully controlled which is an easily accessible task as in case of silver nanoparticles bio-synthesis [119, 120]. These phytochemicals acts as capping agents via acting as binder or stabilizer that blocks the nanopartilces agglomerization or steric hindrance besides, they stabilize the binding of these nanoparticles within the reaction media [121]. For example, the use of *Eruca sativa*, *Spinacia oleracea*, mulberry and *Murraya koenigii* extracts leads to the synthesis of spherical shape silver nanoparticles [122-124]. It is reported that phytochemicals such as phenols, ascorbic acid, resorcinol, umbelliferone, vanillic acid, tannic acid, phenol, rutin, and ellagic acid, flavonoids, alkaloids, acetic acid, D-alanine, and aromatic and aliphatic amines (octodrine) available in the *Nasturtium officinale* leaves extract may act as capping agents in the eco-friendly synthesis of MO_3 nanoparticles, however, amines like aromatic and aliphatic amines in the extract acts as reducing agents [125].

3. Metals and metals oxides characteristics/biological activities

Several metals/metals oxides nanoparticles synthesis methods as well as corresponding biological influences have been reported. Platinum nanoparticles has been reported to exhibit a reducing potential comparable to that of ubiquinone (CoQ10) while oxidizing potential comparable to NADH [126], thus it probably be useful for management of oxidative stress dependent diseases such as Parkinson's disease [127]. This dual activity is attributed to its mutual dual influences on the mitochondrial complex I, hence, reducing the reactive oxygen species formation as well as superoxide, hydrogen peroxide and free radicals scavenging superoxide dismutases (SOD)/catalase like activities [128, 129] which explains their capability to prolong the life span of *Caenorhabditis elegans* nematode [130-132]. In addition, through its antioxidant influence they can prohibit the cigarette smoke induced lung inflammation in mice model [133] as well as enhancing the neurons functions while reducing the cerebral damage next to ischemic stroke [134]. Remarkably platinum nanoparticles have anticancer potential as reported by (Saitoh, *et al*., 2009) to inhibit human tongue cancer cells growth [135] as the nanoparticles in general can binds the DNA via covalent bonds or even adsorption [136].

Furthermore, plasmid DNA is extensively damaged at 125-150μg/ml dose of titanium oxide nanoparticles which probably in part related to the plant extract coat [137]. However, it is reported that titanium oxide nanoparticle has no cytotoxic effects on normal cells as reported for *Desmodium gangeticum* roots extract bio-synthesized nanoparticles that exhibited a non significantly toxic influences on the pigs (LLC-PK1) epithelial cells [25]. Moreover, eco-friendly titanium oxide nanoparticles have been reported to exhibit antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli* [138], besides being effective wound healers in albino rats model [139].As mentioned formerly, titanium oxide particles shape and size are affected by the plant type as well as its extract phytochemicals composition as in case of *Azadirachta indica* that gives rise to anatase structure [140] while the *Ocimum basilicum* L. leaves extract has a hexagonal shape nanoparticles while 50 nm size [141], however, anastase structure was found more cytotoxic thanrutile structures [142]. Thus, depending on these toxicity characteristics it has been reported that titanium oxide nanoparticles have concentration, particle shape, and exposure time dependent cytotoxic influence on human hepatocarcinoma, rat hepatocarcinoma while enhancement of cellular viability in both normal human and rat liver cells [143]. Nevertheless, from opposite prospective, their concentration/time of exposure dependent cell viability enhancing influence on the human osteoblast cell lines encourage the recomondation of the potential wide implication in bone tissue engineering as well as in cosmetics [144].

Furthermore, gold nanoparticles have been thoroughly investigated, and are found to exploit multiply different disease curing influences particularly anticancer activity besides other diagnostic implications as they are easily synthesized, characterized and with accessible surface modification besides, their capability to interact with the –SH- and –NH2-containing molecules [145]. (Ahmad, *et al*., 2013) have synthesized gold nanoparticle surface-biomarker-specific monoclonal anti-bodies and aptamers bio-conjugate for cancer diagnosis [146]. It is used for cancer photothermal therapy through heating gold nanoparticles [147], in addition to drug delivery as these nanoparticles when administered to blood stream they bind to the human albumin that transport them through out the systemic circulation [148], since the human albumin is adsorbed to their surface although albumin chemical atmosphere is altered [149, 150]. Furthermore, the gold nanopartilces stabilized with plant roots and leaves extracts have been reported to exhibit anticancer activity [151]. (Baskar, *et al*., 2018) have reported that fungal asparaginase stabilized 20-50 nm size spherical gold nanocomposites exhibit minor cytotoxic influence ranging from 11.92 to 18.51% cytotoxicity at concentrations ranging from 25 to 1000μg/mL against A2780 ovarian cancer cell line [152]. However, in a previous study, sodium citrate stabilized 20 nm size gold nanoparticles has great A2780 cells proliferation inhibition after 72 hr exposure while those of 5 nm size are of moderate cytotoxic effect and those of 50-100 nm size are of no influence which is consistent to those bio-synthesized using *Nymphaea alba* root extracts [153] as the nanoparticle size decreases as their cytotoxicity increases [154]. In these reports, the nanoparticle physicochemical properties like size, shape, surface charge, time of exposure (after at least 48hrs of exposure), and exposed cell type as well as phytochemical content are significant for their cytotoxicity which are key factors for their cytotoxicity [154] which is in agreement with other reports against the HepG2 cancer and other cancer type [155, 156].

It is necessary to note that gold nanoparticles, particularly those synthesized via eco-friendly methods, have toxic effects on blood proteins including plasma proteins such as albumin [157-161] and hemoglobin [162]. Gold nanoparticles exploit their protein chemical environment alteration related toxicity is attributed to the nanoparticles type, size, shape and metal core dependent conformational changes [163]. It is necessary to note that gold nanoparticles preferentially bind to the cystien and lysine rich proteins leading to alter their chemical structure and hence their biological functions as in case of binding to Heparin-binding growth factors like vascular endothelial 165 as well as basic fibroblast growth factors leading to their inhibition through unfolding of their structures [164]. Thus, the gold nanoparticle have implication in the cancer therapy particularly the metastatic tumors as through their anti-angiogenic activity [165, 166, 167]. In this context, (Arvizo, *et al*., 2013) have reported that the unmodified gold nanoparticles have size and concentration dependent inhibition of tumor cells proliferation through prohibition of MAPK-signaling, reversing of epithelial-mesenchymal transition, up-regulating E-Cadherin, while, down-regulating Snail, N-Cadherin, and Vimentin thus counteracting cancer growth and metastasis [153]. Remarkably, gold nanoparticles also reported to exhibit antibacterial [108, 168, 169] activity while the gold-silver nanoparticles have pharmaceutical [170] as well as biomedical/biosensors applications [171]. Moreover, using *Mentha piperita* L. extract in the green synthesis of gold nanoparticles from $HAuCl_4$ leads to the production of 10-200 nm non-spherical nanoparticles [172] various other plant extract have also been reported for the green synthesis of gold nanoparticles of different implications [173-181].

In most of these green synthesis reports the gold nanoparticulates are chemically synthesized via reduction of the trivalent gold ion Au^{+3} in to elemental gold Au^0 using biocompatible environmentally friendly reducing agents which probably involved in their reported medicinal/biological applications [182-184]. However, (Babu, *et al*, 2013) have proposed two steps bio-reduction for the synthesis of gold nanoparticles using *Bacopa monnieri* leaf ethanolic extract from its salt using UV light. The first involve the reduction of the gold trivalent ion via the extract saponines, alkaloids, sterols and flavonoids content into elemental gold to start nucleation which in turn agglomerate to form clusters. The second step involves the participation of these clusters in further reduction of gold ion into elemental gold that accumulate to form nano-size particles [185, 186], as illustrated in figure (1)quoted from (Babu, *et al*, 2013) report [185]. In addition, both of thylakoids and chloroplasts from green algae and aquatic plants alone or in combination with protiens are also involved in the bio-reduction/nanoparticles synthesis as they are rich in reducing sugars such as glucose and fructose under sun light promotion [187-190]. Nevertheless, no interaction between the isolated thylakoids/chloroplasts and silver ion to produce nanoparticles have been reported to happen at a dark ambient conditions in aqueous solutions [187].

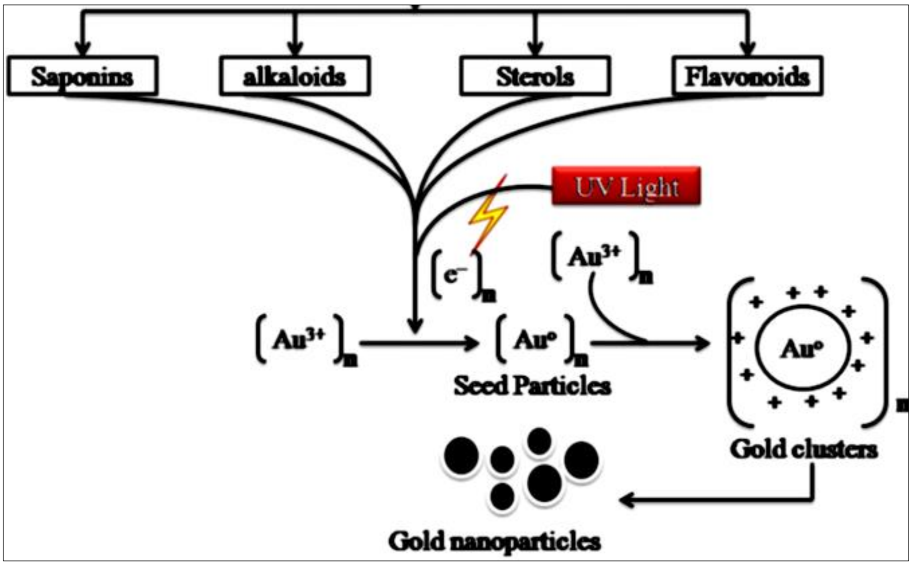

Figure 1 Mechanism by which gold nanoparticles are produced from its gold trivalent salt using UV-light quoted from (Babu, et al, 2013) report[180]

Moreover, copper oxide nanoparticles have been reported exploit various characteristics, however they are mostly of monoclinic crystal structure, as well as multiple biological influences [191] including the anti-inflammatory properties particularly against CFA-induced monoarthritis [192] via counteracting the cytokines release including prostaglandins, serotonins and histamine [193], antimetastatic, antioxidants, drug delivery and anti-fouling [194, 195]. In addition, greenly synthesized copper nanoparticles may exhibit the suitable size, morphology and biocompatibility to exploit antimicrobial activity against gram positive bacteria, gram negative bacteria, and fungi [194-197] as that synthesized using *Tabernaemontana divaricata* leaf extract with anti- *Helicobacter pylori* activity [198]. Various biological substances are used for the synthesis of copper nanoparticles such as oleic acid, gelatin, albumin, starch, and alginate besides algae, bacteria, and plant extracts which also have limited drawbacks [57, 58]. Plant extracts contains many phytochemicals like phenols, flavonoids, tannins, terpenoids, and proteins as reducing and stabilizing agent where the synthesis may happens in room temperature [198-200].

Furthermore, zinc oxide nanoparticles have been reported to exploit antioxidant, antimicrobial [201-206] particularly against gram positive bacteria like staphylococcus aureous and gram negative bacteria like E. coli [207, 208], besides anticancer activity the last two is due to the generation of reactive oxygen species as well as hydrogen peroxide [209-211]. Other mechanism besides the generation of reactive oxygen species related to its antibacterial activity extensively studied in the last two decades is binding to the bacterial cell wall [212, 213] thus enhancing its membrane permeability as well as its adsorption on bacterial proteins [214]. In this context, (Vijayakumar and Vaseeharan, 2018) have reported that zinc oxide nanoparticles exploit potent antibacterial as well as anti-biofilm activity against *Streptococcus mutans* and the gram negative bacteria *Proteus vulgaris* besides anticandial activity at 75 µg/ml concentration [215]. In addition, at 1% concentration both nano-chitosan and silver nanoparticles as well as nano-chitosan and zinc oxide particles combinations has powerful antifungal influence against *Aspargilus niger* with 30 mm diameter zone of inhibition [216]. It is also reported that collagen caated zinc oxide nano-particles exploit anticancer activity against human liver cancer cells (HepG2) and murine macrophage Abelson leukemia virus-transformed cell line (RAW 264.7) at 75 µg/ml concentration [215]. However, the reported antimicrobial and anticancer influences are related to the surface interaction, size dispersion, molecular morphology and reactivity in the solution [203]. In addition, they can promote immune response via enhancing immune cell infiltration even to the brain tissues. Furthermore, zinc nanoparticles have also anti-inflammatory activity against neuronal inflammation via its antioxidant influence, apoptosis inhibitory influence as well as its neurotoxins counteracting activity thus exploiting neuroprotective effect [217-221].

Silver nanoparticles play an extraordinary role in different field of biosciences including biomedicine including DNA sequencing, diagnostic/ probing tool, medical devices coating, optical sensors, orthopedics, cosmotics, antimicrobial influences, anti-inflammatory influence, anticancer influence, antiangiogenic, drug delivery systems design as it exploit enormous biological influences [222-230] besides other pharmaceutical implications [231] are attributed to their unique physicochemical properties of small size along with large surface area [232-235]. One of the prevalently reported broad spectrum antimicrobial activities [236-239] is their antibacterial activity against gram positive like *Bacillus subtilis* and *Staphylococcus aureus* as well as gram negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* [240-246] and fungi [247]. In this context, (Caschera, *et al*. 2020) have reported that Cellulose-capped silver nanoparticles have had exhibited antibacterial influences even against resistant strains particularly against gram positive ones [248] whereas, (Janika, *et al*. 2019) have reported that nanocellulose-aluminium oxyhydroxide ones have exploited efficient antibacterial influence against *E. coli* [249], in addition, the commercially produced silver nanoparticles inhibits *E. coli* at 10 µg/mL concentration as reported by (Li, *et al*. 2009) [239], while at 0.5 dose almost compeletely irradicate *E. coli* [250].

Nevertheless, at the same concentration inhibit *Pseudomonas aeruginosa* at size of 40 nm as reported (Anthony, *et al*. 2014) [251]. Furthermore, silver nanoparticles potentiate the conventionally used antibiotics antimicrobial activity synergistically along with declining the required dose [252, 253] attributed to their reactive oxygen species generation capability particularly the silver ion [254, 255]. It is reported that the aqueous as well as methanolic jujube extracts mediated silver nanoparticles production have demonstrated antibacterial activity [256] while, Oak extract produced nanoparticles have been reported to exhibit antibacterial activity against hospital resistant bacterial strains [257, 258]. Thus, this type of nanoparticles make them suitable for dental application, besides, production of catheters as well as burns wounds management dosage forms [259, 260]. It is also reported that the antibacterial activity of silver nanoparticulates for water sanitation and coast suitable microfilters production [261, 262]. The anti-Gram positive as well as anti- Gram negative bacteria activity is attributed to their morphology and large/volume ratio that maintain their absorption [242].

Moreover, silver nanoparticles exhibit antifungal activity against wide spectrum of pathogenic fungal species including Candida species like Candida albicans and Candida tropical Candida glabrata and their biofilms [263-265]. In this context, (Esteban-Tejeda, *et al*., 2009) have reported that silver nanoparticles have had demonstrated antifungal influence at MIC concentration of 25 μg/ml against *Aspergillus niger* and *Candida albicans* [266] while at size of 20 nm size exhibit good antifungal activity against *Issatchenkia orientalis* [267] on one hand. On the other hand, they have been reported to potentiate fluconazole against *Phoma glomerata*, *Phoma herbarum*, *Fusarium semitectum*, *Trichoderma* sp., and *Candida albicans* [268], besides, enhancing the antibiofilm of the antifungal agent, nystatin or chlorhexidine (CHX) against Candida albicans and Candida glabrata [269]. Remarkably, silver nanoparticles have been reported to exploit antiviral influence [270, 271] against various viral strains including (HIV) and hepatitis B virus (HBV) [272], macrophage (M)-tropic and T-lymphocyte (T)-tropic strains of HIV-1 [273] and H3N2 influenza virus [274] and Peste des petits ruminants virus (PPRV) [275]. Interestingly, (Khandelwal, *et al*., 2014) have reported that tannic acid functionalized silver nanoparticles exhibit HSV-2 infectivity counteracting influence *in vivo* and *in vitro* [276], while, (Lara, *et al*, 2010), have reported that the poly vinyl pyrrolidone (PVP)-coated silver nanoparticles had exploited HIV early stages replication inhibition [271]. It is worthy to note that, (Gaikwad, *et al*., 2013) have reported that the anti-herpes simplex virus (HSV) types 1 and 2 besides the anti-human parainfluenza virus type 3 antiviral activity of silver nanoparticles is attributed to their size as well as zeta potential [277].

However, the various synthesis methods that brought about various silver nanoparticles physicochemical properties, shapes, morphology, sizes, size distribution, surfaces chemistry, composition, coating/capping, agglomeration, and dissolution rate lies behind their biological activities [278] including their interaction dependent various bacterial genus and species growth, cytotoxicity as well as viral replication contracting activity [242, 255, 297-293] in addition to their cytotoxicity along with the type of cells exposed to them [278] as they promotes these nanoparticles physicochemical properties critical bioavaialblity post local or systemic administration as well as their pharmacokinetics [294-297]. Thus, the synthesis conditions of silver nanoparticles should be highly controlled in order to ensure size, morphology and functionality uniformity for diverse medicinal applications [298-303].

In this context, the antibacterial influence of silver nanoparticles are dependent on the morphology, structure, size and shape dependent [297, 304], hence, tiny as well as truncated-triangular ones are more effective than larges nanoparticles [242] similar characteristics are observed for cytotoxicity [305]. In general, silver nanoparticles exhibit an anticancer influence making them useful for both management, diagnosis as well as probing. Their cytotoxic influence is exploited via multiple mechanisms including mitochondrial damage, oxidative stress through reactive oxygen species generation, lactate dehydrogenase leakage, caspases activation, DNA damage, besides opoptosis and autophagy induction via promoting their corresponding genes activation [242, 306]. Silver nitrate cytotoxicity is basically determined by the surface chemical/biological coating materials [307], surface charge particularly the positive charge making them suspended as long as possible in the blood as compared to negatively charged ones [308] and become more suitable for anticancer agents administration [309, 310]. In this context, the silver nanoparticles is uptaken by mean of receptor mediated phagocytosis and exert its cytotoxicity via liberating silver ion as in case of *Albizia adianthifolia* mediated silver nanoparticles that promote apoptotic cell death some of them through caspase pathway induction in lung A549 cells in cell specific manner owed to the lowed interacelluar pH [311, 312]. It also have antiproliferative cytotoxic anticancer activity against cervical carcinoma [313], breast cancer cell lines (MCF-7) [314], T47D cancer cells owed to their higher cellular entrnalization [314], Dalton's lymphoma ascites (DLA) cells in mouse model [292], and MDA-MB-231 human breast cancer cells [315, 316], however, the later one apoptotic death is induced via promoting DNA fragmentation [317]. Silver nanoparticles also exhibit anticancer influences via their cytotoxic/genotoxic influences [318] against NIH 3T3 fibroblast cells, HeLa cells, HCT-116 cell line, MG-63 cell line, acute myeloid leukemia (AML) cells at various sizes,A549, B16, as well as human glioblastoma cells [319-321].

Nevertheless, their antitumor influences through surface adsorption of the cytosolic protiens, increasing the production of the reactive oxygen species in normal human lung cells IMR-90 and human brain cancer cells U251 [110, 255] besides, through causing DNA and/or mitochondrial damage induced apoptosis [322-324]. The intracellularly up taken silver nanoparticles is degraded and oxidized into silver cation that induce cell damage [325] as well as modulates genes in addition to the proinflammatory cytokines [326]. Interestingly, over than 1000 genes regulations are modified such as metallothionein, heat shock protein, and histone families in the epithelial cell line A549 of human ovaries [327]. For example, they activate the p53, p-Erk1/2, and caspase-3 signaling pathways along with prohibiting the Bcl-2 in human breast cancer cells MDA-MB-231 while they mediate apoptotic cancer cells death via p53-dependent pathways activation [328]. Silver nanoparticles are accumulated in the autophagosomes of these cells as well as in B16 mouse melanoma cells, thus, promotes autophagy mediated deaths [329]. While, in HepG2 cells they exert their cytotoxicity through blocking glucose supply, besides, hydrogen peroxide dose-dependent generation [330]. In addition, silver nanoparticles also have been reported to exhibit an anti-angiogenic influence at at 500 nM concentration on bovine retinal endothelial cells (BRECs) [331] probably via caspase-3 and DNA fragmentation promoted vascular endothelial growth factor (VEGF) inhibition through PI3K/Akt pathway inhibition [299, 332] besides, mediating their anti-angiogenic influence via affecting the pigment epithelium derived factor (PEDF) [298] hence blocking new blood microvessels formation. Remarkably, (Baharara, *et al*., 2014) have reported that *Saliva officinalis* mediated synthesized silver nanoparticles have exhibited anti-angiogenic activity at 200 μg/mL concentration demonstrating 50% decline in the cancer tissue newly generated blood vessels of chick chorioalantoic membrane [333].

Furthermore, silver nanoparticles of average size of 23 $\pm$ 2 nm coated with folic acid exhibit excellent folic acid receptor mediated cellular uptake to which anticancer drug, doxorubicin it linked through an electrostatic interaction with an effective drug release and cytotoxicity to lymphoma cells [334, 335]. However, the silver nanoparticle-chitosan-para-aminothiophenol-folic acid nanocomponsate of considerable stability is designed and have demonstrated goodNIH: OVCAR-3 human ovarian cancer cell line targeting as well as enternalization [336] thus exploit anticancer activity [337]. However, a nanocomposate of *Typha angustifolia* extract mediated synthesis silver nanoparticles-anticancer drug salinomycin have been demonstrated to exploit a site specific delivery as well as apoptosis besides, autophagy promoted synergestic cytotoxic influence against human ovarian cancer cells [338]. Furthermore, a nanocomposte of silver nanoparticles embedded in polyethylene based polymeric structure designed as a nanocarrier containing chlorotoxin has exhibited a promoted cellular uptake as well as cytotoxicity against cancer cells [339]. In addition, (AshaRani, *et al*., 2009) have reported that the starch coated silver nanoparticles have induced modification of the cancer cells morphology, decreased cell viability and metabolic activity via inclining the intracellular oxidative stress causing mitochondrial damage and DNA damage leading to cell death in normal human lung fibroblast cells (IMR-90) and human glioblastoma cells (U251) [322] on one hand. On the other hand, others have reported that silica gel embedded silver nanoparticle magnetic doates are designed for targeting breast cancer (SKBR3) as well as floating leukemia cells (SP2/O) [340], others authors have reported that the designed nano-crystals of protein-conjugated silver sulfide exhibit anticancer activity against human hepatocellular carcinoma Bel-7402 and C6 glioma cells that are size dependent [341], third group of authors have reported that the designed chitosan coat nanocarrier have efficiently delivered silver nanoparticles to the HT29 cells which have demonstrated anticancer activity through inclining the intracellular reactive oxygen species [342], however, a third group of authors have reported that nanotriangles of this type of chitosan-silver nanoparticles composates have inclined antineoplastic influence even at low doses [343]. Moreover, silver nanoparticles have implication in cancer phototherapy as well as radiotherapy via intra-tumoral administration of these nanopartilces and their nanocomposates like carbon core composite into the tumor tissues like C6 glioma-bearing rats when using ionization radiation, hence, inducing anticancer cytotoxicity [344, 345]. Finally, silver nanoparticles have been used in combination with the anticancer drug, 5- fluorouracil, syergestically potentiate its anticancer activity via enhancing its uracil phosphoribosyltransferase and non-uracil phosphoribosyltransferase mediated apoptosis in a concentration dependent manner [346].

Surprisingly, silver nanopartilces exploit an anti-inflammatory influence in the inflammatory conditions such as ulcerative colitis [347], thus, it reduces wound inflammation via modulation of fibrinogenic cytokines through down-regulation the expression of these cytokines particularly the pro-inflammatory ones during wound healing phase [348-351] besides, exhibiting apoptotic influence in the inflammatory cells [350, 351].

4. Silver nanoparticles synthesis and mechanism of their antibacterial influence

Various synthetic methods have been reported for silver nanoparticles including chemical sol gel, as well as photo reduction, etc. [352] accompanied by thermal decomposition or radiation [353, 354], however, green biosynthesis of silver nanoparticles [355] for medical fields use is currently extensively used [356, 357] which is pH dependent using biomolecules, bacteria, fungi, algae and plant extracts [118, 316,358-366]. Within the last two decades, plant extracts are extensively used for green biosynthesis of silver nanoparticles such as *Allophylus cobbe*, *Artemisia princeps*, and *Typha angustifolia* [312,367, 368] as they maintain rapid single step synthesis of these nanoparticles [209]. Nevertheless, the extracts of various plant parts such as root, leaf, seed, bark, and fruit have been used as reducing agents for the synthesis of these nanoparticles [369]. In this context, the green plants leaves [370] can be used to synthesize these nanoparticles as an energy preserving, eco-friendly and cheap methods as in case of using *Calliandra haematocephala* leaves extract to synthesize 13.54-91.28 nm nanoparticles [371]. The phytochemical content of the plant extracts like polyphenolic compounds such as tannins and falvonoids as reducing agents while the protein, glucose, polysaccharides and other phytochemicals acts as capping agent [62, 88,109,372, 373] such as using leaf extract of *Diospyros lotus* [374], fruit extract of *Dillena indica* [375], and extract of *Kyllinga brevifolia* [376]. The tanins several hydroxyl groups as well as other phenolic phytochemicals participate in the silver cation reduction into nanoparticles whereas they suffer oxidation from their enolic form to the quinone form. In case of existence of tannin molecules in the plant extract the silver cation oxidizes them then complexed with their enolic form to be completely reduced inside the complex to elemental silver via accepting an electron form an electron donor then leaves the complex in its elemental form while the tannin molecule in its quinonoid form. Nevertheless, it is necessary to note phytochemicals such as flavin binding proteins, terpenols, flavonoids and others are photo-responsive to maintain electron donation spontaneously in the existence of sunlight [377] as illustrated in the figure (2) quated from (Verma, *et al*., 2016) report [378].

Asan example, using of *Allium cepa* as well as *Musa acuminata* extracts for synthesis of 1-10 nm and 15-25 nm size silver nanoparticles respectively [379]. In this regard, silver nanoparticles have been reported to exploit plasmonic influence related tunable optical characteristics [380-382], along with the colloidal stability of the plant phytochemicals capped nanoparticles synthesized using their extracts [340,383], which may explain the extensive investigation intersts as they are found to be suitable for biomedical applications as in case of antimicrobial as well as catalytic implications [72, 355, 384-386]. However, sonochemical activation of nanoparticles have permitted their rapide synthesis at ambient conditions [387, 388], while, others uses leaves extracts such as *Pinus densiflora*, *Diopyros kaki*, *Ginko biloba*, *Magnolia kobus* and *Platanusorientalis* at elevated temeperatures [356]. Remarkably, it is reported that the plant part extract determines silver nanoparticles physicochemical characteristics including the particle size as in case of using of *Verbesinaencelioides* stem and leaves extracts for the synthesis of 37.8 nm and 54.6 nm size silver nanoparticles respectively [389]. In addition, other have reported that using *Azadirachta indica* extract has produced 5-35 nm size spherical nanoparticles [390], others have reported the use of *Sesamum indicum* seeds aqueous extract have producedspherical shape silver nanoparticles of 14 nm avarage size [391], while, a third group of authors have reported that the use of bitter olive fruits extract have produced a hexagonal silver nanoparticles with average size of 20 nm [392]. Furthermore, besides the formely mentioned advantages of green biosynthesis, the ecofriendly bio-synthesis of silver nanoparticles ensures the well-defined size and morphology in addition to maintaining elevated yield, solubility as well as stability [242, 328].

In general the antimicrobial influence of the silver nanoparticle is determined by their size as their activity is enhanced in small size nanoparticles as it inclines the interaction surface area particularly the resistant bacterial strains [228, 276, 303, 393-399]. Their antigram negative activity against E. coli is exhibited via their accumulation in their cell wall [233,400] similarly, yet to a less extent against gram positive especially the methicillin-resistant strain like *S. aureus, Staphylococcus epidermidis, Streptococcus pyogenes* as well as resistant gram negative bacteria *Acinetobacter baumannii, Enterococcus faecalis, Salmonella typhi* and *Klebsiella pneumoniae* [288, 303, 395, 396, 398-403]. In addition, they are effective against biofilm forming bacteria *Pseudomonas aeruginosa* and *Shigella flexneri, Staphylococcus aureus, and Streptococcus pneumonia* [112,404]. There is no exact mechanism contributing to the bactericidal influence of silver nanoparticles, in fact, there is only emphesisms and hypothesis regarding the structural as well as morphological alterations contributing to this influence [297,400]. One of the mechanisms explaining their antibacterial influence is through inhibition of the bacterial respiratory enzyme as they interact with these sulfahydryl containing proteins, hence blocking these pathways besides alteration of bacterial DNA structure alongwith blocking its replication through the binding to the phosphrous group of the genetic materials [243, 405-407] as encountered with *Bacopa monnieri* leaves extract bio-synthesized silver nanoparticles [408].

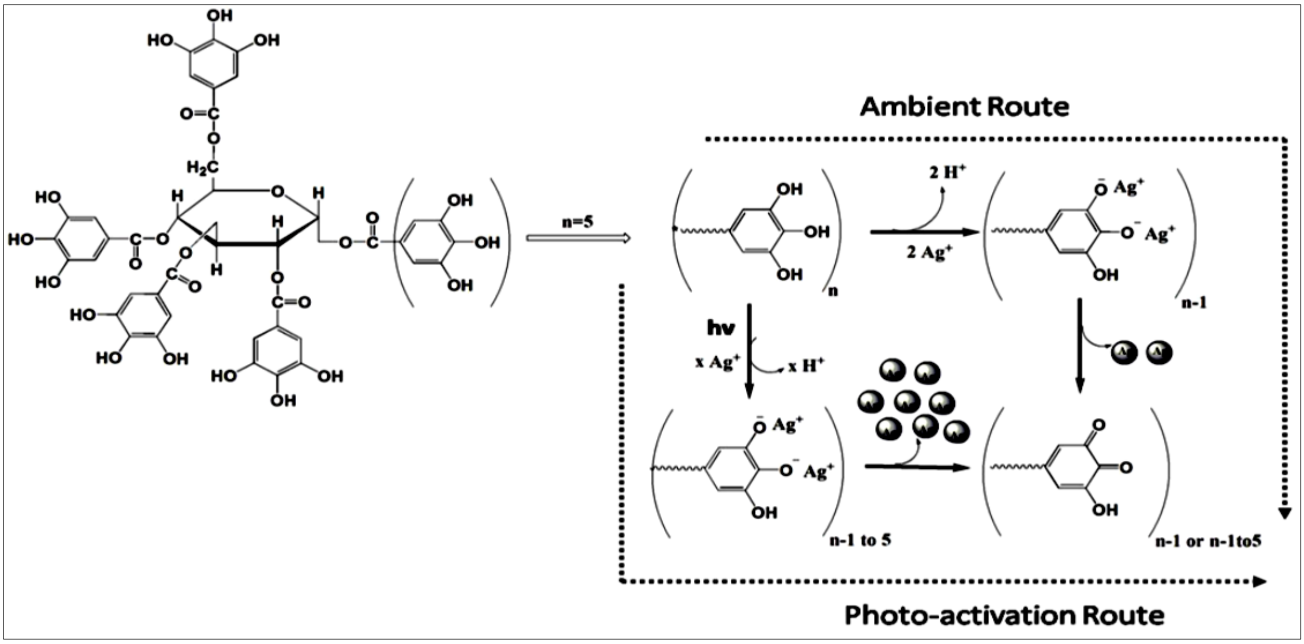

Figure 2 Chemical mechanism of silver cation reduction in to elemental silver by mean of tannins as reported by (Verma, *et al*., 2016) [378]

Silver nanoparticles cause destruction of the cell membrane structure via interacting with structural as well as functional sulfahydril containing proteins leading to the leakage of reducing sugar and proteins outside the bacterial cell via destroying the cell membrane permeability in *E. coli* for example hence bring about cell death [241, 243, 297, 400]. In this content, direct interaction with these intracellular components causing interfering with the metabolic as well as growth signaling pathways through counteracting the tyrosine phosphorylation enzymes involved in the activation of cell viability as well as division critical peptides [409]. A third mechanism involve generation of reactive oxygen species and free radical mediated cell membrane damage via oxidation of the cell membrane along with other baceterial cells content [228, 233,405, 406, 410]. It is necessary to note that the gram negative bacteria are more liable to the silver nanoparticles since they express weaker cell wall explained by the lower peptidoglycan composition as compared to gram positive ones [112, 228, 411, 412]. Nevertheless, silver nanoparticles is less effective against resistant bacteria and viable cells [407], hence, gram positive bacteria as they contains thicker alongwith smoother cell wall. Remarkably, the silver ion released from the silver nanoparticles accumulate in the cell wall via electrostatic attraction to start cell wall/cell membrane destruction, however, the irregular shape samller size ones have greater tendency to accumulate as well as bringing about cell damage [413-415]. Finally, the silver nanoparticles of <10 nm is much effective bactericidal agent as they have greater tendency to liberate silver cation that interact with the negatively charged cell wall/membrane which damages their permeability then leakes intracellularly and then via blocking the respiratory chain enzymes leading to the generation of the reactive oxygen species including hydroxyl radical and superoxide anions hence, affecting the cell survival and functions via denaturation of the bacterial protiens and DNA besides, their capability to binds the essential proteins SH functionality [297,415-426]. Therefore, (Shrivastava *et al*, 2007) have reported that silver nanoparticles have the capability to adhere to *E. coli* cell wall then leakes inside the bacterial cell hence destroying the cell wall, inhibiting phosphate cellular uptake via promoting the release ofphosphate, mannitol, succinate, proline, and glutamine from the cell thus killing the bacterial cells [409, 427].

5. Conclusion

Investigations within the field of nanotechnology approach is extremely reported within the last two decades. However, within the last decade the investigations in this approach have found the way to the medicinal as well as pharmaceutical fields. In the medical fields, the investigations have reported various beneficial biological infuluences particularly antimicrobial as well as antineoplastic influences besides, potentially advantageous application in the diagnostic radioscanning use. While, in the pharmaceutical fields the investigators have postulated the fesiability of the nanoparticulates for site specific drug delivery particularly the antitumor drugs. According to this survey, it has been thoroughly reported that the plant parts extracts, especially the aqueous extracts, phytochemicals specifically the reducing phenolic as well as polyphenolic phytochemicals are very convenient ecofriendly, safe, and economic reducing/capping agents for their production. Nevertheless, from the biological point of view beside the role of phytochemicals in nanoparticles production they are also involved in exhibiting their biological activity. The most remarkable reported biological activity is the antibacterial activity particularly against gram negative bacteria of silver nanoparticals besides, the antineoplastic activity of gold and platinium nanoparticles against tumors. The outcomes of this survey encourage us to conclude the fesibility of investment in the investigations in this approach.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors confirm that there is no conflict of interests.

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