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PLANT-MEDIATED GREEN SYNTHESIS OF SILVER NANOPARTICLES FOR BIOMEDICAL APPLICATIONS: CHALLENGES AND OPPORTUNITIES

SUMAIRA ANJUM, BILAL HAIDER ABBASI* AND ZABTA KHAN SHINWARI

Department of Biotechnology, Quaid-i-Azam University, Islamabad 45320, Pakistan
**Correspondence author's email: bhabbasi@qau.edu.pk; Tel & Fax: 0092-51-90644121*

Abstract

Metallic nanoparticles are an emerging class of functional materials, revolutionizing all domains of human life making nanotechnology, a promising arena for biomedical applications. Among the metallic nanoparticles, Silver nanoparticles (AgNPs) represent one of the most comprehensively studied nanomaterials. The current development and execution of new technologies have led to new era, the nano-revolution which discloses the role of plants in green synthesis of nanoparticles and have drawn fairly an undeniable attention with a vision of synthesizing stable and eco-friendly nanoparticles. Employing plant extracts toward synthesis of AgNPs are emerging as advantageous over other conventional methods due to low-cost, energy-efficient, non-hazardous, and environmentally tolerable along with the manifestation of broad variability of biomolecules in plants, which can act as reducing and capping agents. Biologically synthesized AgNPs have upsurge applications in various sectors such as electronics, clothing, food industry, paints, sunscreens, cosmetics, biosensing, medicines, drug delivery and medical devices. Broad-spectrum bioactivities of AgNPs indicate their potential to solve many microbial resistance problems. The antibacterial, antifungal, antiviral, antiprotozoal, anti-inflammatory and anticancer activities of AgNPs have recently engrossed the attention of scientists. The aim of the present review is to discuss the plant mediated green synthesis of AgNPs and mechanistic aspects involved in reduction and stabilization of AgNPs. Methods of AgNPs characterization are reviewed and broad-spectrum multifunctional activities of AgNPs and their potential biomedical applications are discussed. This review also focuses on the assessment of impending human and ecosystem deathtraps associated with increased utilization of AgNPs and the safety issues concerning their biomedical applications.

Key words: Silver nanoparticles, Green synthesis, Plant extracts, Biomedical applications, Toxicity.

Introduction

The concepts that planted nanotechnology as a new field were first introduced by a famous physicist R. P. Feynman in his conversation "There's", in which he described the probability of synthesis by the use of direct manipulation of atoms (Feynman 1995). However, the advent of nanotechnology as a field arisen through the junction of Drexler's theoretical and public work in the 1980s, who established and propagated a conceptual framework for nanotechnology (Drexler 1986). In modern era, nanotechnology is the manufacturing of functional systems at the atomic scale and the use of matter with at least one dimension ranging from 1 to 100nm in size. As defined by size, nanotechnology is unsurprisingly very vast, including all fields of science as sundry as surface science, organic chemistry, functional biology, semiconductor physics, electronics and micro-fabrication(Saini *et al*., 2010). Nanoscale materials have received huge attention in the last decade, because their properties and structure vary considerably from those of atoms and molecules in addition to bulk materials (Zargar *et al*., 2014). The synthesis of nanoscale materials with the preferred qualities is one of the most exhilarating aspects in recent nanoscience and nanotechnology. At the present time, nanoscale metallic particles synthesis (silver, gold, zine etc.) is the most captivating area of exploration for researchers, due to miscellaneous array of their applications in the fields of molecular biology, material sciences, biomedical engineering, electronics and medicines (Kanipandian *et al*., 2013).

Synthesis of metallic nanoparticles is gigantic and an expanding area due to their potential applicability in numerous fields such as electronics, optoelectronics, functional biology, drug delivery, antimicrobial and biosensors (Bhattacharyya *et al*., 2009). The synthesis of metallic nanoparticles is classified by two approaches; top-down and bottom-up. The bulk materials are reduced in size (10-100 nm) in top-down methods while in bottom-up approach the preparatory materials are grown-up to larger structures (nano) by linking atoms or molecules together(Kavitha *et al*., 2013). Numerous research techniques are presented by the scientists for the production of metallic nanoparticles through different physical and chemical methods. But, these synthetic methods involving different chemicals are expensive and may lead to the presence of noxious chemical species tangled on the surface of nanoparticles, which may have adversarial effects in various biological and biomedical applications (Mittal *et al*., 2014). This increases the growing need to develop environment friendly procedures for synthesis of nanoparticles through "green synthesis" and other new biological approaches.

Green nanotechnology is an area of interest having substantial attention in present scenario with chief objective of facilitating the synthesis of nanotechnology-based products, environment friendly and innocuous for all beings with sustainable profitable viability (Bar *et al*., 2009a; Chung *et al*., 2016). The ''green synthesis'' of metallic nanoparticles receives more attention due to their uncommon optical, photo-chemical, chemical and electrical properties (Mohanpuria *et al*., 2008). The green methods of nanoparticle synthesis using biological entities like bacteria (Navazi *et al*., 2010), yeast(Kowshik *et al*., 2003), fungi (Hemath *et al*., 2010)and plants are stated to be clean, non-hazardous, in-expensive and environmentally tolerable when compared to chemical methods. The use of microorganisms or plant-based biomimetic methods consume very little energy, generate very little pollution (if any), and mostly operate under conditions of normal temperature and pressure (Bhat *et al*., 2013; Nazeruddin *et al*., 2014a). Among the several biological methods of

nanoparticle synthesis, microbe facilitated synthesis of nanoparticles is, however, not commercially viable as they involve maintenance of highly hygienic conditions and very complex processes of maintaining microbial cultures (Raj *et al*., 2006). Additionally, the microorganisms require a relatively longer incubation time for the reduction of metallic ions as compared to plants which attained such reduction in a much shorter time due to the presence of water soluble phytochemicals which act as reducing agents (Ghaffari-Moghaddam and Hadi-Dabanlou 2014). Synthesis of metallic nanoparticles by plant extracts is the most implemented method of green, eco-friendly fabrication of nanoparticles and also has a distinctive advantage that the plants are extensively distributed, easily accessible, safe to handle and act as a source of numerous metabolites (Kavitha; Baker; 2013). The use of plant extracts is also beneficial over microorganisms due to the easiness of scale up, the less bio-hazardous and intricate process of maintaining cell cultures(Rai *et al*., 2011). Plant-based methods also do not require sophisticated controls in maintaining the bio-agents as are necessitated in the case of microorganisms (Baker *et al*., 2013). In this respect, they represent an advantage similar to the other 'green' procedures that are emerging, such as microwave-assisted nanoparticle synthesis (Galletti *et al*., 2013).

Among the metallic nanoparticles, Silver nanoparticles (AgNPs) represent one of the most comprehensively studied nano-materials and the most favorite target of the above stated 'green' methods, which fascinate scientists due to their distinctive optical, catalytic, sensing, antimicrobial properties and easily reduction of Ag^{+} salts to form zero valent silver (Ag^{0}). Gold nanoparticles are also of a significant interest, although to a much lesser extent than silver. Other metallic and inorganic nanoparticles are exemplified by a small number of reports. The plasmon resonances of AgNPs are of primary scientific interest due to their applicability in biosensing, surface enhanced Raman scattering spectroscopy, nano-photonics, solar energy harvesting, and plasmonic nano-laser construction. AgNPs reveal marvelous applications in various sectors such as biomedical field, optical receptors, intercalation materials for electric batteries, filters, bio-labelling, anti-microbial agents and biosensors (Sharma *et al*., 2013). They are also largely applied in shampoos, detergents, cosmetics, soaps, toothpastes, medical and therapeutic products and are hence directly come across by human systems (Banerjee *et al*., 2014). There has been a number of experiments executed on the synthesis of AgNPs using various plants extract in the field of pharmacological applications and biological industries. Due to the emergence of infectious diseases and antibiotic resistance in pathogenic microorganisms, the pharmaceutical industries and scientists are looking for new antimicrobial agents and the AgNPs are the most promising contenders for antimicrobial action. Broad-spectrum bioactivities of AgNPs make them promising agents not only in fighting infections but also in tackling serious problem of tumors and, particularly, multi-drug resistant cancer cells (Nazeruddin *et al*., 2014b).

The aim of the present review is to discuss green synthesis of AgNPs using various reported plants extract used up-till now and how different plants extract mediate the synthesis of AgNPs by exploiting their naturally existing phytochemicals which act as reducing as well as stabilizing agents (Mittal; Bhaumik 2014). We emphasize on the characterization and applications of AgNPs especially in the field of biomedical sciences including their effects on different types of pathogenic micro and macro organisms, such as bacteria, viruses and fungi to provide possible explanation of their mode of action. This review also focus on the assessment of impending human and ecosystem deathtraps associated with increased utilization of AgNPs and the safety issues concerning biomedical applications of AgNPs.

Plant mediated synthesis of AgNPs: Now it is the time to cram about the secrets existing in the nature and its products which leads to the development of innovations in the synthetic processes of metallic nanoparticles. In recent times, nanoparticle synthesis is among the most fascinating scientific areas of investigation, and there is emergent attention to produce nanoparticles using plants extract. The plant systems can be used both intracellularly and extracellularly for the production of different metallic nanoparticles (Chandran *et al*., 2006; Dinesh *et al*., 2012; Gardea-Torresdey *et al*., 2003; Harris & Bali 2007; Haverkamp & Marshall 2009; Jha & Prasad 2010; Renugadevi & Aswini, 2012; Hesgazy *et al*., 2015). The intracellular methods for the production of nanoparticles comprise growing plants in metal-rich media (Gardea-Torresdey *et al*., 2001), metal-rich soil (Haverkamp *et al*., 2006) and metal-rich hydroponic solution, etc (Harris and Bali 2007). Whereas, extracellular methods for the production of nanoparticles include use of leaves extract prepared by boiling or grinding of leaves in water or ethanol (Ankamwar *et al*., 2005; Parashar *et al*., 2009; Shankar *et al*., 2004). Usage of various plant parts like fruits (Li *et al*., 2007), stems (Armendariz *et al*., 2004), bark (Sathishkumar *et al*., 2009), seeds (Bar *et al*., 2009b), latex (Bar; Bhui 2009a)and callus (Mude *et al*., 2009)have been reported for the green synthesis of metallic nanoparticles.

The first report of the plant used in the extracellular synthesis of nanoparticles is credited to *Medicago sativa* (alfalfa) which is capable of synthesizing silver and gold nanoparticles by exploiting its biomolecules (Gardea-Torresdey; Gomez 2003). Since then, huge attention has been given to plants as a source of nanoparticles synthesis. Most of the reports converse the synthesis of AgNPs by plants that were recognized to be stable than nanoparticles synthesized by other methods (Baker; Rakshith 2013). Table 1 represents various plant species capable of synthesizing AgNPs that have been reported in recent year's literature (2010 to date). Plant extracts are believed to act as reducing as well as capping agents in the synthesis of nanoparticle. The nature of plant extract effects the kind of nanoparticles synthesized in a highly critical manner with the source of plant extract being the most vital factor affecting the morphology of synthesized nanoparticles (Mukunthan & Balaji, 2012). Interestingly, this is so because different plant extracts contain different amounts of biochemical reducing agents (Li *et al*., 2011). In the production of nanoparticles from the plant extracts, the plant extract is basically mixed with a solution of metal salt at room temperature. The reaction is completed within few minutes and, as a result of biochemical reduction, the metals are converted from their mono or divalent oxidation states to zero-valent states. This marks the formation of nanoparticles, which is physically indicated through the

color change observed in the culture medium vessel. Synthesis of gold, silver, and a number of other metal based nanoparticles have been reported in this manner (Safaepour *et al*., 2009).

In this review paper we emphasize on the synthesis of AgNPs due to its biomedical applications. The general methodology involved in the synthesis of AgNPs by different plant extracts (Fig. 1). First of all the required plant extract is prepared by boiling the plant material in water or ethanol. The prepared plant extract is incubated with desired concentration of $AgNO_3$ solution in a fixed ratio. The color of the mixture start changing from colorless to brownish with the passage of time which is the first visual indication of the synthesis of AgNPs. The synthesis of AgNPs is initially confirmed by UV–Visible spectrophotometry which gives different distinctive peaks of absorptions between 420 to 460 nm, due to the surface plasma resonance (SPR) of the AgNPs produced. After that further characterization of AgNPs is carried out with other analytical techniques to find out the various characteristics of synthesized AgNPs (Baker; Rakshith 2013; Gandhi; Sirisha 2014; Logeswari; Silambarasan 2013; Qu; Sun 2014).

Several factors affect the reduction process of silver ions into the AgNPs such as temperature, concentration of plant extracts, concentration of $AgNO_3$ solution, pH, incubation time, etc (Rai & Yadav 2013). The pH of the reaction mixture is an imperative factor that is considered to affect the size and shape of nanoparticles. Satishkumar *et al*., (2009) synthesized AgNPs using *Cinnamomum zeylanicum* leaf extract at different pH values ranging from 1 to 11. They reported that the AgNPs of large size having ellipsoidal shape were observed at lower pH, while AgNPs with small size having spherical shape were observed at higher pH (Sathishkumar; Sneha 2009). The aqueous solution of AgNPs exhibit different SPR behavior at different pH values that was enlightened in terms of size and size distribution of AgNPs (Singh *et al*., 2009). One of the most exciting aspects of AgNPs synthesis by plants extract is the fact that this procedure takes place at ambient temperature. However, the size and shape of nanoparticles is determined by the temperature of the reaction mixture which is a precarious factor. Song and Kim (2008) assessed the biosynthesis of AgNPs at different temperatures (25, 55 and 95°C). They reported that the gradual increase in temperature of reaction mixture results in an increase in the rate of biosynthesis in addition to the transformation of silver ions to AgNPs. The final transformation of silver ions was 60% at 25°C which increases to almost 100% at 55°C. However, the size of AgNPs decreases with increase in temperature (25°C-95°C) from 50 nm to 16nm. The change in concentration of the plants extract also affects the synthesis of AgNPs (Song & Kim 2008). Bar *et al*., (2009) studied the effect of different concentrations of latex and $AgNO_3$ on synthesis of AgNPs. Authors used different concentrations of latex (2, 3 and 5%) for synthesis of AgNPs among which latex concentration (3%) was found to be most effectual for biosynthesis. Effect of different concentrations of $AgNO_3$ (1, 3 and 5 mM) was also studied and it was observed the intensity of SPR band increases with the increase in the concentration of $AgNO_3$. The results also revealed that an increase in the intensity of SPR also resulted in the increase of concentration of AgNPs (Bar; Bhui 2009a). Consequently, different factors direct the synthesis of AgNPs by changing their size and shape.

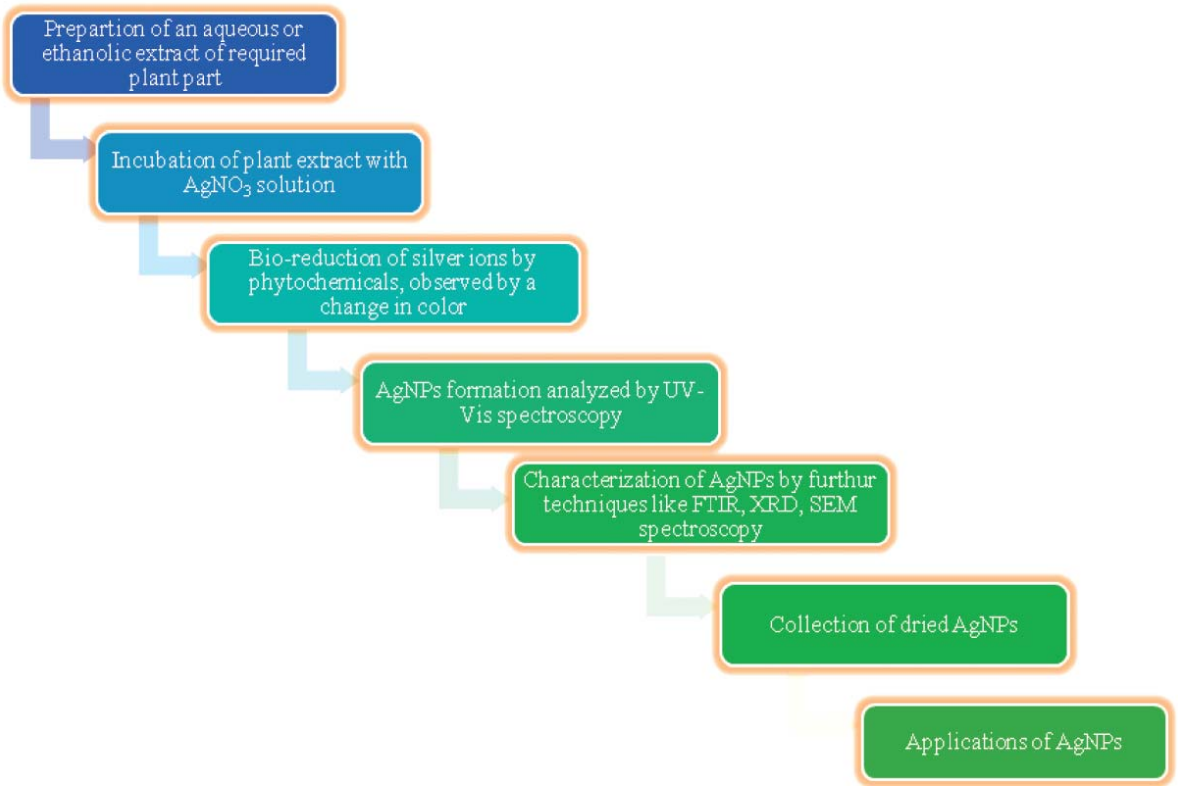


Fig. 1. Steps involved in the synthesis of AgNPs from plant extracts.

Table 1. Representing plants reported in literature (2010 to date) for synthesis of AgNPs

S. #	Plant	Size	Shape	Possible biomolecules involved	Reference
1.	*Linum usitatissimum*	19-24 nm	Face centered cubic	Polyphenols and flavonoids	Anjum and Abbasi, (2016a)
2.	*Tinospora cordifolia*	30 nm	Spherical	Amide and flavonoids	Selvam *et al.* (2016)
3.	*Artemisia marschalliana*	5-50 nm	Spherical	hydroxyl, amide, and carbonyl groups	Salehi *et al.* (2016)
4.	*Phlomis bracteosa*	22.41 nm	Face centered cubic	Flavonoids (5, 7, 2-trihydroxyflavone)	Anjum and Abbasi, (2016b)
5.	*Ceropegia thwaitesii*	100 nm	Face centered cubic	Triterpenoids and methoxy groups	Muthukrishnan *et al.* (2015)
6.	*Eucalyptus oleosa*	21 nm	Face centered cubic	-	Pourmortazavi *et al.* (2015)
7.	*Nyctanthes arbortristis*	5-20 nm	Face centered cubic	Flavonoids, tannins, terpenoids and saponins	Gogoi *et al.* (2015)
8.	*Achillea biebersteinii*	5-35 nm	Hexagonal, pentagonal and spherical	Polysaccharides, polyphenols and proteins	Baharara *et al.* (2014)
9.	*Vitex negundo* L.	> 20 nm	Face centered cubic	Flavonoids	Zargar *et al.* (2014)
10.	*Plukenetia volubilis* L.	4-25 nm	Spherical	Cellulose, Pectin and polyphenols	Kumar *et al.* (2014)
11.	*Syzygium cumini*	10-15 nm	Face-centered-cubic	Flavonoids	Mittal *et al.* (2014)
12.	*Boerhaavia diffusa*	25 nm	Spherical and face centered cubic	Polyols and nitrates	Vijay Kumar *et al.* (2014)
13.	*Caesalpinia coriaria*	40-52 nm	Triangular	Tannins	Jeeva *et al.* (2014)
14.	*Dalbergia* spinose	18 ± 4 nm	Spherical	Reducing sugars and flavonoids	Muniyappan and Nagarajan, (2014)
15.	*Saraca indica*	12 nm	Face centered cubic	Flavanones and terpenoids	Vidhu and Philip, (2014)
16.	*Peltophorum pterocarpum*	40-85 nm	Face centered cubic	Flavonoids	Balamurugan *et al.* (2014)
17.	*Berberis lyceum*	8-100 nm	Oval, rectangular and spherical	Nicotinamide adenine dinucleotide	Mehmood *et al.* (2014)
18.	*Brassica rapa* L.	16.14 nm	Spherical	Amine and aliphatic esters	Narayanan and Park, (2014)
19.	*Melia azedarach.* L.	30-45 nm	Spherical	Flavonoids	Mehmood *et al.* (2014)
20.	*Rhynchotechum ellipticum*	0.51-0.73 µm	Spherical	Polyphenols, alkaloids and terpenoids	Hazarika *et al.* (2014)
21.	*Chrysanthemum indicum*	37.71-71.99 nm	Spherical	Flavonoids, terpenoids and glycosides	Arokiyaraj *et al.* (2014)
22.	*Agrimoniae herba*	30.34 nm	Spherical	Flavonoids and phenolics	Qu *et al.* (2014)
23.	*Parmotrema praesorediosum*	19 nm	Face centered cubic	-	Mie *et al.* (2014)
24.	*Ficus elastic*	50-60 nm	Spherical	Proteins	Gandhi *et al.* (2014)
25.	*Alternanthera dentate*	10–80 nm	Face centered cubic	Flavanoids and terpenoids	Kumar *et al.* (2014)
26.	*S. tricobatum*	48 nm		Alkaloids and flavonoids	Logeswari *et al.* (2013)
	S. cumini	34 nm		Tannins	
	C. asiatica	43 nm		Tannins and steroids	
	C. sinensis	33 nm	-	Alkaloids and flavonoids	
27.	*Pelargonium graveolens*	47 nm	Face centered cubic	Proteins	Pandian *et al.* (2013)
28.	*Lycopersicon esculentum* Mill.	33.6 nm	-	Aromatic and amines	Asmathunisha and Kathiresan, (2013)
29.	*Rumex hymenosepalus*	2-40 nm	Face centered cubic and hexagonal	Polyphenol	Rodriguez-Leon *et al.* (2013)
30.	*Eriobotrya japonica*	18 nm	Face centered cubic	Carboxylic compounds	Awwad *et al.* (2013)
31.	*Ocimum sanctum*	16.87 nm	Face centered cubic	Linalools and terpenes	Ramteke *et al.* (2013)
32.	*Pimenta dioica*	20-45 nm	-	Ployols	Geetha *et al.* (2013)
33.	*Ocimum basilicum* (L.)	88 nm	Spherical	Anthocyanins and flavonoids	Jayapriya and Lalitha, (2013)
34.	*Cocos nucifera*	23±2 nm	Face centered cubic	Coconut-coir	Roopan *et al.* (2013)

Table 1. (Cont'd.).

S. #	Plant	Size	Shape	Possible biomolecules involved	Reference
35.	*Phyllostachys aurea*	13-3.5 nm	Spherical and Hexagonal	Flavonoids and phenolic acids	Yasin *et al.* (2013)
36.	*Ceratonia siliqua*	5-40 nm	Face centered cubic	Proteins	Awwad *et al.* (2013)
37.	*Artocarpus heterophyllus*	10.78 nm	Irregular shape	Amino acids and amide groups	Jagtap and Bapat, (2013)
38.	*Hibiscus cannabinus* L.	9 nm	Spherical	Ascorbic acid	Bindhu and Umadevi, (2013)
39.	*Cleistanthus collinus*	20-40 nm	Spherical	Proteins and amide compounds	Kanipandian *et al.* (2013)
40.	*Coleus aromaticus* Lour.	40-50 nm	Face centered cubic	Flavonoids	Vanaja and Annadurai, (2013)
41.	*Piper nigrum*	40- 60 nm	-	Piperine	Mani *et al.* (2012)
42.	*Aristolochia Bracteata*	7.2 nm	Mixed crystalline structure	Aromatic compounds	Raj *et al.* (2012)
43.	*Hyacinthus orientalis*	61.45 nm	-	Polyphenols	Bunghez *et al.* (2012)
44.	*Prthenium hysterophorus*	10 nm	Face centered cubic	Hydroxyflavones & catechins	Kumar, (2012)
45.	*Elaeagnus latifolia*	30-50 nm	Face centered cubic	-	Phanjom *et al.* (2012)
46.	*P. granatum*	5-20 nm	-	Polyalcohols	Chauhan *et al.* (2012)
47.	*Chromolaena odorata*	40-70 nm	Anisotropic crystals	Dicarboxylic aminoacids & sulfonyl chloride	Geetha *et al.* (2012)
48.	*Pisonia grandis*	20-150 nm	Face centered cubic	Pinitol and allantoin	Firdhouse *et al.* (2012)
49.	*Callicarpa maingayi*	12.40 ±3.27 nm	Face centered cubic	Aldehydes and amines compounds	Shameli *et al.* (2012)
50.	*Allium sativum* L.	4 .4 ± 1.5 nm	Spherical	Sucrose and fructose	White *et al.* (2012)
51.	*Andrographis paniculata* Nees.	28 nm	Cubic and hexagonal	Hydroxyflavones and catechins	Sulochana *et al.* (2012)
52.	*Astragalus gummifer* Labill	13.1±1.0 nm	Spherical	Proteins	Kora and Arunachalam, (2012)
53.	*Dioscorea bulbifera* L.	8–20 nm	Face centered cubic	Polyphenols or flavonoids	Ghosh *et al.* (2012)
54.	*Glycyrrhiza Glabra* L.	20 nm	Face centered cubic	Flavonoids, terpenoids and thiamine	Dinesh *et al.* (2012)
55.	*Hydrilla verticilata* (L.f.) Royle.	65.55 nm	Spherical	Proteins	Sable *et al.* (2012)
56.	*Morinda pubescens* L.	25-50 nm	Orthorhombic	Hydroxyflavones and catechins	Mary and Inbathamizh, (2012)
57.	*Pedilanthus tithymaloides* (L) Poit.	15-30 nm	Face centered cubic	Proteins and enzymes	Sundaravadivelan *et al.* (2012)
58.	*Solanum xanthocarpum* L.	10 nm	Spherical	Phenolics, alkaloids and sugars	Amin *et al.* (2012)
59.	*Leonuri herba* L.	9.9-13 nm	Spherical	Polyphenols and hydroxyl	Rang Im *et al.* (2012)
60.	*Cardiospermum helicacabum*	5-50 nm	Spherical	Flavonoids	Mitra *et al.* (2012)
61.	*Phyllanthus amaru*	32-53 nm	-	Alkyl halides and alkaloids	Annamalai *et al.* (2011)
62.	*Cleome viscosa*	50-70 nm	Face centered cubic	Amide compounds	Banu *et al.* (2011)
63.	*Murraya koenigii*	10-25 nm	Face centered cubic	-	Christensen *et al.* (2011)
64.	*Ipomea carnea*	30-130 nm	Face centered cubic	Alkaloids with polyphenols	Daniel *et al.* (2011)
65.	*Achyranthus aspera* L.	20-30 nm	Face centered cubic	Polyols	Daniel *et al.* (2011)
66.	*Citrullus colocynthis* L.	31nm	Spherical	Polyphenols with aromatic ring and amide compounds	Satyavani *et al.* (2011)
67.	*Mentha piperita*	90 nm	Spherical	Amide groups	Ali *et al.* (2011)
68.	*Memecylon edule*	50-90 nm	Square	Triterpenes, tannins and flavonoids.	Elavazhagan and Arunachalam, (2011)
69.	*Coriandrum sativum*	26 nm	Face centered cubic	Proteins and carbonyl compounds	Sathyavathi *et al.* (2010)
70.	*Trianthema decandra*	15 nm	Face centered cubic	Hydroxyflavones and catechins	Geethalaksh and Sarada, (2010)
71.	*Solanum torvum*	14 nm	Face centered cubic	Carboxylate ions	Govindaraju *et al.* (2010)
72.	*Tanacetum vulgare*	16 nm	Face centered cubic	Phenol, ester and amide groups	Dubey *et al.* (2010)

Mechanistic aspects involved in reduction and stabilization of AgNPs by plant extracts: Synthesis of AgNPs by plant extracts is under meticulous research; although, a precise mechanism involved in the synthesis of AgNPs using plant extracts has not yet been clarified. However, several suppositious mechanisms have been suggested (Daniel; Ayyappan 2011; Kumar; Palanichamy 2014b; Ponarulselvam *et al*., 2012; Rai *et al*., 2009; Thakkar *et al*., 2010). Every new plant species has some excellent biomolecule in its genome through which it brings about the biochemical reduction. Huang *et al*. (2007) synthesize AgNPs by exploiting biomolecules present in *Cinnamomum camphora* leaf extract and verified by Fourier Transform Infrared Spectroscopy (FTIR). Different functional groups such as ether (–C–O–C), alcohol (–C–O–H), and carbonyl (–C=O–) derived from a number of heterocyclic compounds were observed. In the FTIR spectra, these biologically active compounds are assumed to act as reducing and stabilizing agents for the AgNPs (Huang *et al*., 2007a). Zargar *et al*. (2014) indicated the presence of flavonoids that are supposed to be responsible for the reduction of silver ions in to silver during the synthesis of AgNPs by using an aqueous extract of *Vitex negundo* L. FTIR spectra indicate the presence of phenolic hydroxyl groups in the structure of flavonoids, which essentially substantiates the presence of friedelin, lupeol, and b-sitosterol groups, acting as reducing agents *Vitex negundo*L. extract(Zargar; Shameli 2014).

Li *et al*. (2007) used aqueous extract of *Capsicum annuum* L. for the synthesis of AgNPs which revealed that the proteins having amine groups play an important regulatory role (reduction) during the formation of AgNPs in the solutions(Li; Shen 2007). AgNPs were prepared via plant extracts from xerophytes (*Bryophyllum* sp.), hydrophytes (*Hydrilla* sp.) and mesophytes (*Cyperus* sp.) by Jha *et al*., (2009). For xerophytes (*Bryophyllum* sp.), a mechanistic scheme was proposed in which the oxidative decarboxylation of malic acid take place to produce pyruvate. Besides this, pyruvate produces phosphorenol pyruvate (PEP) that is used in the glycolytic pathway in the presence of PEP carboxykinase. Emodin, which belongs to anthraquinone, also go through redial tautomerization that results in the reduction of silver ions (Jha *et al*., 2009). For mesophytes (*Cyperus* sp.) a different mechanism for AgNPs production was suggested, in which reduction of silver ions might result due to tautomerization of benzoquinones like cyperquinone (type I), dietchequinone (type II), and remirin (type III). On the other hand ascorbate is oxidized in antioxidative reactions and the enzyme dehydroascorbate (DHA) reductase catalyzes the re-reduction of DHA to ascorbate in hydrophytes (*Potamogeton* sp. or *Hydrilla* sp.). Consequently, Jha *et al.* (2009) proposed conceivable mechanisms for AgNPs production by using various plant extracts which act as reducing as well as capping agents based on different metabolite present in them(Jha; Prasad 2009).

Jain *et al*., (2009) synthesize the AgNPs by using Papaya fruit extract and by FTIR analysis they proposed that Polyols are chiefly involved in the reduction of silver ions by oxidizing themselves to unsaturated carbonyl groups. The FTIR analysis of AgNPs synthesized by leaf extract of *Piper nigrum* exhibit intense absorption peaks corresponding to N–H stretching of primary amine, asymmetric and symmetric stretching of alkanes, which denotes the presence of hydrogen bonded OH stretching of carboxylic acids in the leaf extract, which may be a reducing agent accountable for the synthesis of AgNPs (Jain *et al*., 2009). Shankar *et al*., (2003) synthesized AgNPs by using geranium leaf extract and concluded that the terpenoids (containing hydroxyl groups) like citronellol and geraniol present in the leaf extract are oxidized to carbonyl groups resulting in the reduction of silver ions(Shankar *et al*., 2003). Supportive to this result, Safaepour *et al.* (2009) synthesize AgNPs by the direct use of geraniol extract which is a strong reducing agent and showed that geraniol have capability of reduction of silver ions independently. Concentrating on the role of peptides, Jatropha latex (from *Jatropha curcas*) was used as reducing and stabilizing agent to form AgNPs (Bar; Bhui 2009a). The chief peptide elements of the latex present in this plant are curcacycline A (cyclic octapeptide) and curcacycline B (cyclic nonapeptide) which are responsible for the reduction and capping of AgNPs formed. The FTIR analysis also confirmed this by showing a decrease in the intensity of the secondary amine band and shifting of the stretching vibration of the amino group (NH)-C=O before and after the formation of AgNPs. These results revealed that the cyclic peptides curcacycline A and B are responsible for the reduction as well as in the stabilization of silver ions to AgNPs (Bar; Bhui 2009b).

Pelargonium graveolens leaf extract possess various heterocyclic compounds which are soluble in water such as alkaloids, flavonoids which act as the capping agents for the synthesis of AgNPs and the presence of oxygen atoms assist in the stabilization of AgNPs by enabling the absorption of heterocyclic compounds on nanoparticles surfaces. FTIR results showed that the carbonyl group present in the amino acid residues and proteins has the stronger capability of binding with metal representing that the proteins could possibly form a layer wrapping the metal nanoparticles (capping of AgNPs) to avoid agglomeration in medium (Pandian; Marimuthu 2013). In another study the FTIR analysis was carried out to identify the possible plant metabolites responsible for the reduction of the silver ions and capping of the AgNPs synthesized by *Aristolochia bracteata* leaf extract (Raj; Anarkali 2012). Demonstrative spectra obtained from AgNPs manifests the presence of different functional groups like secondary alcohol (O-H stretch, H-bonded), Alkanes (-C-H- stretching), Alkene (C=C- stretching), Aromatic (C=C-C- stretching), Alkane (-C-H bending), Ether (C-O stretching) and Alkene (=C-H bending) which are responsible for reduction of silver ions. Spectra also revealed that the proteins (amino or carboxyl groups) present in the plant extract can bind to AgNPs and thus acting as capping agent for AgNPs (Raj; Anarkali 2012). Asmathunisha & Kathiresan (2013) synthesize the AgNPs from *Lycopersicon esculentum* Mill leaf extract and reported that, the AgNPs seemed to be associated with some chemical compounds having hydroxyl and carbonyl groups and suggested that these compounds are likely to be phenols and their derivatives which act as reducing agents and furthermore they suggest that the capping ligand of the AgNPs may be an aromatic compound or amines present in the plant extract(Asmathunisha & Kathiresan 2013).

Kora & Arunachalam (2012) used an aqueous extract of *Astragalus gummifer* to produce AgNPs. FTIR spectral analysis revealed a large band shifts in the FTIR spectra

corresponding to various Polyols, alcoholic and carbonyl groups. This confirms that the oxidation of the hydroxyl and carbonyl groups results in the reduction of silver ions. On the basis of these band shifts, they also concluded that both hydroxyl and carbonyl groups of *Astragalus gummifer* are involved in the synthesis of AgNPs (Kora and Arunachalam 2012). Banerjee *et al.* (2014) synthesized AgNPs from the extracts of *Musa balbisiana* (banana), *Azadirachta indica* (neem) and *Ocimum tenuiflorum* (black tulsi). For characterization of AgNPs produced from each type of plant extract, FTIR analysis was carried out. The representative spectra of FTIR analysis showed the stretching in the peaks of ether linkages (-C-O-C-), germinal methyls (-C-O-) and alkenes groups (-C=C-), proposing that the compounds like flavonoids and terpenoids are involved in capping and stabilization of AgNPs(Banerjee; Satapathy 2014). Yadav & Rai (2011) produced AgNPs from leaf extract of *Holarrhena antidysenterica* which contain many bioactive compounds like conessine, holarhimine and kurchine (Kumar *et al*., 2007). In case of *Holarrhena antidysenterica* extract, terpenoids (cardenolides) are supposed to be surface active molecules and the reduction of metal ions is possibly assisted by terpenoids present in the leaf extract. Thus, in the mechanistic study Yadav & Rai (2011) propose that the process of bio-reduction might have occurred due to the redox activities of ascorbic/dehydro-ascorbic acid and terpenoids (cardenolides), leading to the reduction of silver ions present in the solution. Also, the proteins are found to act as capping and stabilizing agent for AgNPs (Yadav & Rai 2011). Vanaja & Annadurai (2013) synthesized AgNPs by using *Coleus aromaticus* leaf extract, which acts as a reducing and stabilizing agent due to the manifestation of aromatic amine, phenolic groups, amide groups and secondary alcohols for the synthesis of AgNPs (Vanaja & bAnnadurai, 2013). The synthesis of AgNPs was accomplished by using *Syzygium cumini* fruit extract at room temperature by Mittal *et al*. (2014). For the identification of possible biomolecules involved in the capping and stabilization of AgNPs, FTIR analysis was carried out to. The absorption peaks in FTIR spectra revealed the strong stretching of (C–N) aromatic and aliphatic amines, amide bond (NH=C-) due to carbonyl stretch in proteins and hydroxyl (OH) stretching in alcohols, phenolics and flavonoids. The absorption patterns of synthesized AgNPs, fruit extract isolated flavonoids and a flavonoid standard (quercetin) were similar in nature demonstrating the covering of flavonoids on the surface of AgNPs and thereby stabilizing AgNPs(Mittal; Bhaumik 2014).

All extracts of *Desmodium triflorum* contain various classes of compounds like flavonoids, polyphenols, triterpenoid, saponins, sterols, triterpenes, proteins and reducing sugars. Leaf extract of *Desmodium triflorum* was used for the synthesis of AgNPs and two possible mechanisms of reduction of silver ions were proposed by Ahmad *et al*., (2011). The first probable mechanism involved in reduction is glycolysis which converts glucose into pyruvate and hydrogen ion along with the release of free energy in the form the high-energy compounds, ATP (adenosine triphosphate) and NAD (nicotinamide adenine dinuleotide). NAD is a powerful reducing agent involved in redox reactions, transferring electrons from one reaction to another and this might have led to conversion of silver ions to silver. The second mechanism suggested by Ahmad *et al*. (2011) for the reduction of silver ions could be due to the presence of anti-oxidative substances like ascorbate (vitamin C) which are water soluble and present in large amount in all parts of plants. Ascorbic acid is a strong reducing agent and can reduce reactive oxygen species (ROS) into ascorbate radical and free electron. This free electron is responsible for the reduction of silver ions to silver (Shahverdi *et al*., 2011). Vidhu & Philip (2014) prepared AgNPs from *Saraca indicia* flowers which contain flavanones and terpenoids. They proposed a possible reduction mechanism of silver ions by the involvement of terpenoids which carry out the reduction by oxidation of aldehyde groups (H-C=O) in the molecules to carboxylic acids (-COOH). Probably by dealings through carbonyl groups or pi-electrons in the absence of other powerful chelating agents, flavonoids and terpenoids could be adsorbed on the surface of AgNPs and thus act as capping agents(Vidhu & Philip 2014). Seed extract of *Coriandrum sativum* was used for the synthesis of AgNPs by Nazeruddin *et al.,* (2014). A comprehensive study on literature of *Coriandrum sativum* disclose that the chief components of the plant are coriandrol, sucrose, maleic acid, tannin, volatile oil, phenolic, fatty acids and minerals, etc. Nazeruddin *et al*. (2014) proposed a possible mechanism involved in the reduction of silver ions by phenolic compounds which have capability of binding with metals. The roots of numerous plants contain high level of phenolic and flavonoids compounds which may deactivate ions by chelating e.g; luteolin is a common flavone present in the aerial part of some plants which freely liberates reactive hydrogen during the formation of -enol form which is responsible for the transformation of silver ions to silver (zero valent)(Nazeruddin; Prasad 2014a) (Table 2).

FTIR analysis was carried out for the identification of possible biomolecules present in *Glycyrrhiza glabra* root involved in the reduction of silver ions and capping of nanoparticles leading to effective stabilization of the AgNPs (Dinesh; Karthikeyan 2012). FTIR spectral results revealed that most of the bands were representative of flavonoids and terpenoids and vibrational bands corresponding to bonds such as –C=C, –C–O–C, –C=O, –C–O and –C–N were derived from the plant metabolites like thiamine, flavonoids and terpenoids present in *Glycyrrhiza glabra* roots. Hence, from FTIR analysis it may be assumed that these biomolecules are accountable for capping and proficient stabilization of AgNPs (Dinesh; Karthikeyan 2012). Sable *et al*., (2012) described the synthesis of AgNPs by using an aquatic plant *Hydrilla verticilata.* For identification of the potential biomolecules involved in the reduction of silver ions and capping of the AgNPs by protein, FTIR analysis was carried out. Representative spectra of obtained AgNPs were evident of absorption peaks of respective functional groups (amide and amino) in the infrared region (IR) of the electromagnetic spectrum and indicate the presence of stabilized protein molecules (Basavaraja *et al*., 2007; Sable; Gaikwad 2012). Carob (*Ceratonia siliqua*) leaf extract was used for the synthesis of AgNPs and FTIR study was carried out to find the potential biomolecules involved in reduction and capping of AgNPs (Awwad; Salem 2013a). FTIR study shows that the carboxyl (−C=O), amine (N-H), and hydroxyl (−OH) groups in carob leaf extract are chiefly

involved in reduction of silver ions. The FTIR spectroscopic study also revealed that the protein present in carob leaf extract is responsible for the stabilization of AgNPs by preventing agglomeration. The amino acid residues containing carbonyl group also has a robust chelating ability with metal, signifying the formation of a covering layer on AgNPs and thus acting as a capping agent to avoid agglomeration in the aqueous medium (Awwad; Salem 2013a). Firdhouse *et al.,* (2012) produced AgNPs from ethanolic extract of leaves of *Pisonia grandis* (*Firdhouse; Lalitha 2012).* The presence of metabolites like pinitol and allantoin in *Pisonia grandis* was already reported (Shubashini *et al*., 2011). A probable method of pinitol and allantoin with $AgNO_3$ producing AgNPs was proposed by Firdhouse *et al*., (2012). According to proposed mechanism the allantoin and pinitol undergo tautomerism and proton shifting takes place within the molecule. The silver ion is attacked by the oxygen atom of the hydroxyl group attached with the ring of allantion and pinitol. This complex molecule become unstable and hydroxyl group reduces the silver ion (Ag^+) to silver (Ag^0), thus producing stable AgNPs (Firdhouse; Lalitha 2012). *Camellia sinensis* (green tea) extract has been used for the biosynthesis of AgNPs at ambient conditions, which act as a reducing as well as capping agent (Vilchis-Nestor *et al*., 2008). FTIR analysis revealed that the phenolic compounds like the ophylline and caffeine existing in the *Camellia sinensis* extract are accountable for the stabilization of AgNPs. Mainly the plant secondary metabolites acts as reducing agents in synthesis of any metallic nanoparticles (Fazal *et al*., 2016; Khan *et al*., 2014)

Characterization of AgNPs: Characterization of metallic nanoparticles is crucial to develop understanding about nanoparticle synthesis and applications. A wide range of different analytical techniques, primarily drawn from materials science are used for characterization of nanoparticles such as scanning electron microscopy (SEM), transmission electron microscopy (TEM),powder x-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF), dynamic light scattering (DLS), atomic force microscopy (AFM)and ultraviolet -visible spectroscopy(Kirthika *et al*., 2014;Kim *et al*., 2014; Mehmood; Murtaza 2014a; Schaffer *et al*., 2009; Shahverdi; Shakibaie 2011; Strasser *et al*., 2010). Various parameters of nanoparticles including particle size, crystallinity, shape, orientation, fractal dimensions, surface area, pore size, intercalation and dispersion are determined by these techniques (Kholoud *et al*., 2010). Primary confirmation of formation of nanoparticles is carried out by UV-Visible spectroscopic technique (Desai *et al*., 2012). In UV-Visible characterization of AgNPs, spectrophotometric absorption values in the wavelength ranges of 420–460 nm are used (Huang & Yang 2004). It uses light in the visible and nearby ranges (near-infrared) and the absorption or reflectance in the visible range directly affects the apparent color of the chemicals involved. It is well-known that the spectrum surface plasmon resonance of nanoparticles is affected by the size, shape, free electron density, interparticle interactions and surrounding medium which revealed that UV-Visible spectroscopy is a competent tool for observing the electron injection and aggregation of nanoparticles (Ghosh & Pal, 2007).

The phase variety and crystal structure of synthesized AgNPs is determined by X-ray diffraction (XRD) spectroscopy (Ramteke; Chakrabarti 2013). XRD is a powerful tool that is used for the identification of atomic and molecular structure of a crystal. Crystalline atoms diffract a beam of incident X rays in many specific directions and by determining the angles and intensities of these diffracted beams, a crystallographer can produce a three-dimensional (3-D) image of the density of electrons within the crystal. From this electron density we can determined the mean positions of the atoms, their chemical bonds, as well as their disorder in crystal (Ealick 2000; Noginov *et al*., 2006). FTIR technique is used to identify the possible biomolecules present in plant extracts involved in reduction and capping of silver ions, leading to efficient stabilization of the synthesized AgNPs (Hazarika; Phukan 2014). FTIR spectrometer instantaneously collects spectral data in a wide spectral range which confers a momentous advantage over a dispersive spectrometer which measures intensity in a narrow range of wavelengths (Prati *et al*., 2010). Precise determination of AgNPs size, size distributions and size dimensions is vital not only for characterization of important size-dependent properties but also for many other imperative scientific applications. TEM and SEM are the universally employed techniques for measuring the size of nanoparticles. This is due to their ability of providing all information directly related to the morphology of metallic nanoparticles (Bowers Ii *et al*., 2009). As compared with the SEM, TEM has a 1000 fold higher resolution power (Eppler *et al*., 2000), even 0.8 nm-sized particle image has been clearly obtained by TEM (Yao *et al*., 2010). Scanning probe microscopy (SPM), which consist of atomic force microscopy (AFM) and scanning tunneling microscopy (STM) can offer a 3-D resolution as high as 0.1 nm (Bai 2000). Mass spectrometry (MS) is extensively used to find out the molecular weights of nanoparticles by ionizing the sample and cataloguing the ionic species on the basis of their mass-to-charge (m/e) ratios. In order to find out the molecular weights of nanoparticles, the particles should not decay during the course of ionization or detection processes, and the array of dimensions should be large enough to quantitate higher molecular weight nanoparticles (Dharmaratne *et al*., 2009). Laser desorption ionization (LDI), Matrix assisted laser desorption ionization (MALDI), and electrospray ionization (ESI) techniques are used to avoid nanoparticles fragmentation during ionization and detection (Dass *et al*., 2008; Navin *et al*., 2009). Additionally, a time-of-flight (TOF) analyzer can detect heavy masses over a range of 300 kilo-Dalton (kDa). Joining the advantages of ESI or MALDI for ionization and TOF for detection, MALDI-TOF and ESI-TOF are the most suitable methods for characterizing AgNPs by mass spectrometry (Kim; Hackett 2014).

Biological activities and biomedical applications of AgNPs: Nanoparticles synthesized by Green based principle are known to have enormous applications in the area of molecular biology and medicine in contrast to the nanoparticles synthesized by physical and chemical procedures which involve the use of noxious solvents, chemical species, and surfactants. Various reducing agents (chemicals) and stabilizing agents (surfactants) used in chemical synthetic procedures are known to produce lethal wastes but in green based principle, there is no use of harsh

solvents/surfactants or noxious chemicals. Naturally plants contain a broad variety of phyto-biomolecules which act as reducing as well as stabilizing agents, characteristically increasing the biomedical applications of nanoparticles synthesized by green based principle (Baker; Rakshith 2013). Plant mediated synthesized nanoparticles are more superior with reference to their *In vivo* biomedical applications in contrast to the chemically synthesized nanoparticles, owing to the fact that the cellular growth components required for cell growth and proliferation are irreversibly agglomerated due to chemical similarity among them by the biomolecules naturally existing in the plants such as amino acid, proteins, salts, alkaloids, flavonoids, etc (White; Kerscher 2012). Some reports also recommend that the use of nanoparticles synthesized by plant extracts in nano-medicines is more superlative, compatible and friendly due to their stability in numerous biological media (Shukla *et al*., 2008; Ahmed *et al*., 2016). Owing to their exclusive physical and chemical properties and high surface area to volume ratio, AgNPs possess many important biological activities (Duran and Marcato 2013; Kumar; Smita 2014a; Rai and Ingle 2012). In particular, AgNPs have found their application in the treatment of wounds (Atiyeh *et al*., 2007; Rigo *et al*., 2013), burns (Elliott 2010), in development of nano-containing materials for bone implants (Marsich *et al*., 2013), dental materials (Meehan *et al*., 2009)and as anti-bacterial(Dar *et al*., 2013; Jeeva; Thiyagarajan 2014; Muniyappan and Nagarajan 2014; Nazeruddin; Prasad 2014b), antifungal (Dar; Ingle 2013; Kaur *et al*., 2012; Xu *et al*., 2013), antivirals (Fayaz *et al*., 2012), anti-protozoans (Adhikari *et al*., 2013), anti-arthropods (Subarani *et al*., 2013), anti-larvicidal (Veerakumar *et al*., 2014) and anti-cancerous agents (Devaraj *et al*., 2013; Jeyaraj *et al*., 2013).

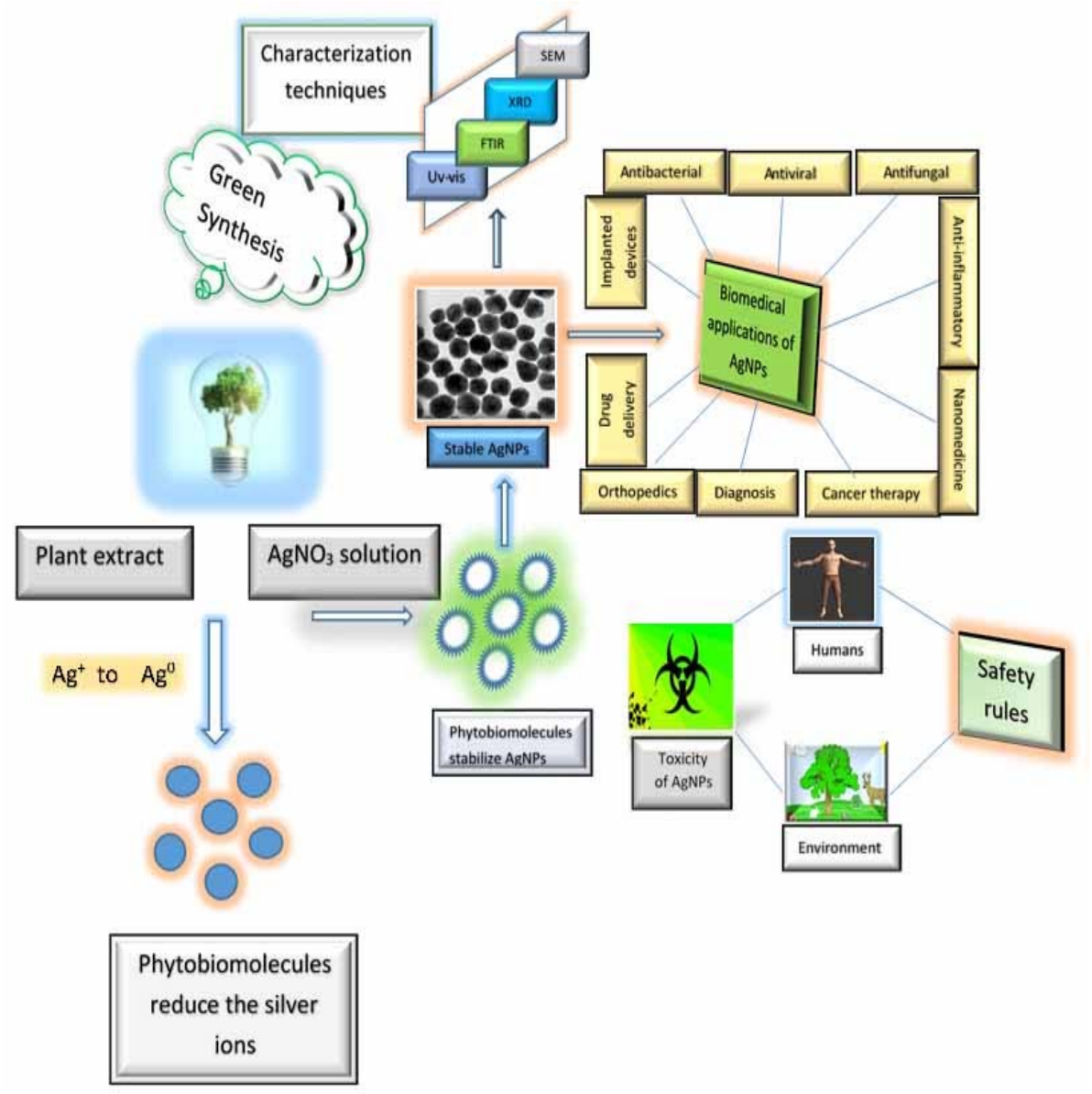
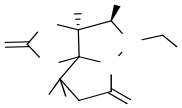
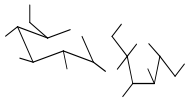
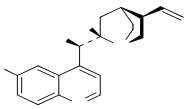
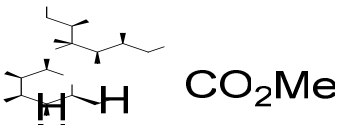
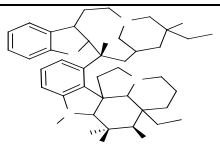
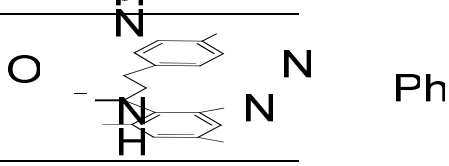
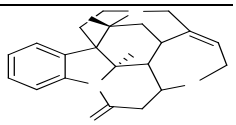
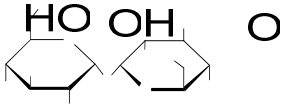
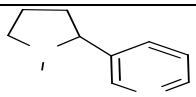
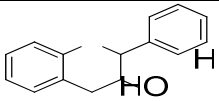
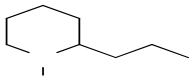
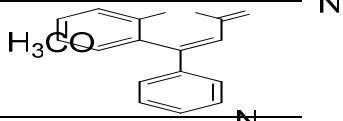
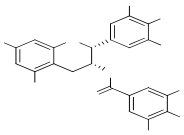
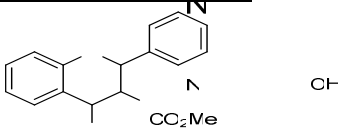
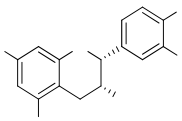
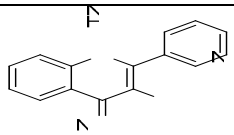
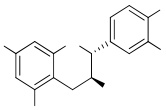
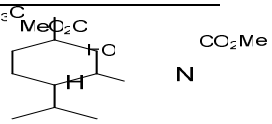
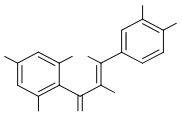
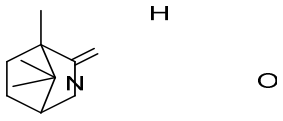
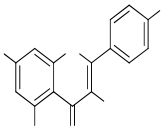
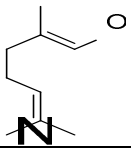
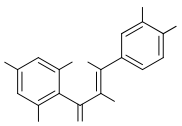
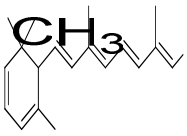


Fig. 2. Biomedical applications of green synthesized AgNPs.

Table 2. Different classes of biomolecules involved in reduction and stabilization of AgNPs.

Class	Compound	Structure	Class	Compound	Structure
Alkaloid	Saxitoxin		**Polyols**	Sucrose	
	Quinine			Maltitol	
	Vinblastine			Phloretin	
	Strychnine			Trehalose	
	Nicotine			Flavan-3-ol	
	Coniine			Neoflavonoid	
Polyphenols	Epigallocatechi-3- Gallate		**Flavonoids**	Leucoanthocyanidin	
	(-) - Epicatechin			3- Hydroxyflavone	
	(+) - Catechin			Menthol	
	Quercetin			Camphor	
	Kaempferol		**Terpenoids**	Geraniol	
	Isorhamnetin			Retinol	

Antibacterial activity of AgNPs: Before the advent of AgNPs, $AgNO_3$ was used as an effective antibacterial agent clinically (Chen and Schluesener 2008; Li *et al*., 2008; Monteiro *et al*., 2009). Later, the use of silver agents ($AgNO_3$, AgCl and free silver) decreases with the emergence of antibiotics which came into fame during the last era. Recently, Silver again returned to eminence due to emergence of antibiotic resistant bacteria which are developed due to the excessive use of antibiotics (Madhumathi *et al*., 2010; Rai; Yadav 2009). With the development of nanotechnology, the interest and awareness in the use of the antibacterial efficacy of AgNPs has been relighted. A comparative study of Nanosilver, $AgNO_3$ and AgCl exposed that AgNPs have higher antibacterial activity than free silver ions (Choi *et al*., 2008). The AgNPs have been proven as an active bactericide against a wide range of bacteria comprising both Gram-negative and Gram-positive bacteria (Jones & Hoek, 2010; Nazeruddin; Prasad, 2014b), which includes numerous highly pathogenic bacterial strains.

To investigate the antibacterial properties of AgNPs, Kim *et al*. (2007) performed an experiment by using a model of both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria. Results showed that the growth of *E. coli* is inhibited at a very low concentration (3.3 nM) of AgNPs which is ten times less than the minimum inhibitory concentration (MIC) of *S. aureus* (33 nM) (Kim *et al*., 2007). By using *Aspergillus niger* isolated from soil, Gade *et al.* (2008) produced AgNPs and reported that the AgNPs with 20 nm in size were cytotoxic to *E. coli.* Further the TEM analysis showed that after a few minutes in contact with AgNPs, the bacterial membrane was completely ruptured, indicating the high efficacy of AgNPs owing to unique property of large surface area to volume ratio (Raffi *et al*., 2008). In another study, Shrivastava *et al*. (2007) reported the robust antibacterial activity and increased stability of AgNPs (10–15 nm) against a number of drug resistant bacterial strains. It was inferred from many reports that the antibacterial activity of AgNPs is dose-dependent and is more prominent against Gram-negative as compared to Gram-positive bacteria (Kumar; Pammi 2014c; Mallikarjuna *et al*., 2011; Roopan; Madhumitha 2012). The AgNPs were found to show potential antimicrobial activity against multidrug resistant Gram-positive (*Escherichia coli* and *Pseudomonas aeruginosa*) and Gram-negative (*Klebsiella pneumonia* and *Staphylococcus aureus*) clinically isolated human pathogens (Jeeva; Thiyagarajan 2014). Similarly, the antibacterial activity of AgNPs was evaluated on pathogenic *Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia* and, *Enterococcus faecalis* by agar diffusion method. The zone of inhibition was caused by the AgNPs at different concentrations but AgNPs are found to be highly toxic against bacteria at concentration of 50 ppm (Kumar; Pammi 2014c). Martinez- Gutierrez *et al*. (2012) reported that AgNPs ranging in size (20–25 nm) have strong antibacterial effects against five clinically isolated pathogenic strains (*E. coli, E. faecalis, P. aeruginosa, S. aureus*, and *S. maltophilia*), generally allied with internal medical devices. The authors reported that all the clinically isolated pathogenic bacterial strains were sensitive to the AgNPs with MIC ranging between 1 to 3.5 µg of AgNPs/mL (Martinez-Gutierrez *et al*., 2012).

Different parameters effect the antibacterial activity of AgNPs such as size and shape, exposure time, concentration of the silver, the types of compounds (Bugla-Płoskonska *et al*., 2007; Sadeghi *et al*., 2012)and the target microorganisms (Guzman *et al*., 2011). The silver content in any of sliver reagent ($AgNO_3$, AgCl) has to be high enough to inhibit the growth of bacterial cells (MIC) or kill 99.9% of them (minimal bactericidal concentration, MBC). AgNPs are superior for use as a medical factor than silver ions due to their prolonged activity. Kvitek *et al*. (2008) used different types of surfactants (sodium dodecyl sulfate-SDS and polyoxyethylenesorbitane monooleate-Tween 80), and polymer (polyvinylpyrrolidone-PVP 360) for stabilization of AgNPs and revealed that the antibacterial activity of AgNPs is also dependent on surface modifications (surfactant/polymers). These AgNPs were tested against a number of pathogenic bacterial strains including *S. aureus, E. faecalis, E. coli* and *P. aeruginosa*, and many other strains isolated from human clinical samples such as *P. aeruginosa*, *S. epidermidis* (methicillin-susceptible), *S. epidermidis* (methicillin-resistant), *E. faecium* (vancomycin-resistant),and *K. pneumonia.* The results revealed a significant boosting in the antibacterial activity of the AgNPs when modified by using SDS as compared to Tween 80 and PVP (Kvitek *et al*., 2008).

So far, there are many studies reported in literature emphasizing the antibacterial effects of AgNPs against a broad spectrum of bacterial strains (Banerjee; Satapathy 2014; Mehmood; Murtaza 2014a; Mie; Samsudin 2014). Although various studies suggested different antibacterial mechanisms of action of AgNPs to explain the underlying mechanism of growth inhibition, membrane distraction, and death of bacterial cells (Kim; Kuk, 2007; Kumar; Pammi, 2014c; Pal *et al*., 2007; Sondi and Salopek-Sondi 2004), but unfortunately the precise mechanism of action has not been fully understood. Jones & Hoek (2010) in their review(Jones & Hoek, 2010) briefly concise three most generally acknowledged antibacterial mechanisms of action of AgNPs as follows:

(i) Bacteria can uptake free silver ions which leads to the interruption of ATP synthesis and DNA replication.

(ii) Generation of ROS by AgNPs or silver ion.

(iii) AgNPs may direct damage to cell membranes.

However, there is copious conflict in the literature about which mechanism of AgNPs has the foremost antibacterial effects, but now researchers believe that it is a collective effect in which each mechanism contributes equally to provide broad spectrum antibacterial activities of AgNPs. Moreover, bacterial resistance to free silver ions is tremendously erratic (Silver 2003); highlighting the manifestation of multiple bactericidal mechanisms acting in collaboration (Chaloupka *et al*., 2010).

Antifungal activity of AgNPs: In present scenario, a rapid increase in microbes have been observed that are resistant to conventional antibiotics due to excessive use of antibiotics. Specifically, the frequency of infections

triggered by opportunistic fungal strains has been augmented melodramatically, and the AgNPs have materialized themselves as a potential antifungal agents. Unambiguously, fungal infections are most frequent in immune compromised patients due to human immunodeficiency viral infections. Numerous reports are available in the literature presenting the antimicrobial effects of AgNPs but their antifungal effects remain unmapped (Rai *et al*., 2014). As a fungicide, AgNPs are more effective as compared to free silver against a wide range of commonly found fungi such as *Aspergillus, Candida* and *Saccharomyces* (Ramya and Subapriya 2012). Kim *et al.* (2008) reported the antifungal activity of chemically synthesized AgNPs against 44 strains of six fungal species (*Candida albicans, C. tropicalis, C. glabrata, C. parapsilosis, C. krusei* and *Trichophyton mentagrophytes*). AgNPs showed potent activity against various strains of *T. mentagrophytes* and *Candida* sp (Kim *et al*., 2008). Roe *et al*., (2008) have verified the antifungal activity of AgNPs (100 nm) which were coated on plastic catheters. Results revealed that the growth inhibition of *C. albicans* was nearly complete(Roe *et al*., 2008). The antifungal properties of AgNPs synthesized by using slightly amended Tollens process was investigated by Panacek *et al*., (2009). Results showed the minimum inhibition concentrations (MIC) was 0.21 mg/L against *C. albicans* growth by using naked AgNPs, and 0.04 mg/L by using AgNPs stabilized with SDS. Antifungal activity of AgNPs in combination with heterocyclic compounds like pyrazolo, thiazolidine, tetrazolo, phthalazine and pyridazine derivatives were studied against *Aspergillu sflavus* and *C. albicans*. Results confirmed enhanced antifungal activity of AgNPs in combination with heterocyclic compounds as compared to heterocyclic compounds alone (Kandile *et al*., 2010). Savithramma *et al*. (2011) synthesized AgNPs using extract of *Boswelliao valifoliolata, Shoreatum buggaia* and *Svensonia hyderobadensis*) and evaluated their antifungal activity against *A. flavus, A. niger, Curvularia* sp., *Fusarium* sp. and *Rhizopus* sp. The results showed that all the three nanoparticles synthesized from different medicinal plants have significant activity against all the tested fungi. Among these, nanoparticles synthesized from *Svensonia hyderobadensis* showed higher activity as compared to AgNPs synthesized using two other plants(*Boswelliao valifoliolata* and, *Shoreatum buggaia*)(Savithramma *et al*., 2011).

Noorbakhsh *et al*., (2011) studied the antifungal properties of AgNPs against commonly found fungal strains and reported that the MIC of AgNPs against *C. albicans* and *C. glabrata* was ranging from 0.4 to 3.3 µg/ml(Noorbakhsh *et al*., 2011). Kaur *et al*. (2012) studied potential antifungal properties of AgNPs against *Rhizoctonia solani*, *Alternaria flavus*, and *Alternaria alternata* from chickpea seeds (Kaur; Thakur 2012). In another study, Arjun and Bholay (2012) also reported activity of AgNPs against *C.albicans, Trichophytonrubrum* and *Aspergillus fumigatus*(Arjun and Bholay 2012). In an extensive study, Xu *et al.* (2013) evaluated AgNPs and kanamycin against 216 strains of fungi from patients suffering from severe keratitis. These included 112 isolates of *Fusarium*, 82 isolates of *Aspergillus* and 10 *Alternaria* isolates. The authors reported that AgNPs demonstrated higher activity compared to kanamycin(Xu; Gao 2013). Recently, Dar *et al*. (2013) reported the remarkable antimicrobial activity of AgNPs synthesized from *Cryphonectria* sp. against *S. aureus, E. coli, Salmonella typhi* and *C. albicans*, concluding that AgNPs can be used as potential antifungal agents(Dar; Ingle 2013). In spite of various reports on antifungal activity of AgNPs, a precise mechanism of such effect has not been reported. One of possible explanations is destruction of membrane integrity of fungi and inhibition of budding process in yeasts (Kim *et al*., 2009).

Antiviral activity of AgNPs: AgNPs have received tremendous attention for their antibacterial activities, but the antiviral properties of AgNPs remain an unripen area (Galdiero *et al*., 2014). Now-a-days, effective and innocuous antiviral therapies are available which leads to a remarkable improvement in the lives of a large number of patients; nevertheless, viruses still characterize as one of the most prominent causes of the disease and death worldwide (Rai; Kon 2014). Moreover, emerging and re-emerging viral diseases are a major threat to human and veterinary health (Howard and Fletcher 2012). Therefore, there is a greater need to develop new and unique treatment options with antiviral agents, which can also overcome the problem of antiviral resistance. Owing to their potential antiviral activity, AgNPs are evolving as one of the best options for the management of viral infections (Galdiero *et al*., 2011). AgNPs are effective antifungal agents against a broad spectrum of viruses presenting a few chances of raising resistance as compared to conventional antivirals and have received huge attention due to their specific intrinsic properties, especially since they have shown antiviral efficacy against several viruses regardless of the specific family. Three key aspects can be comprehended from the studies conducted so far on the antiviral properties of AgNPs:

(i) AgNPs have revealed antiviral activity against a number of viruses infecting both prokaryotic (De-Gusseme *et al*., 2010; Narasimha 2012)and eukaryotic organisms, making them a true broad-spectrum antiviral agent.
(ii) Viral inhibition depends on the size of AgNPs (generally small AgNPs, 25 nm or less, resulted more active in viral infectivity inhibition) (Lara *et al*., 2010; Speshock *et al*., 2010).
(iii) Initial viral infection might be a common time frame where AgNPs may employ their antiviral effects by influencing the left over viral replication cycles (Speshock; Murdock 2010).

However, a precise mechanism of AgNPs antiviral activity and an exact stage of infection at which AgNPs exert antiviral activity have yet to be determined.

Several studies have analyzed the behavior of naked (without a capping agent) AgNPs in inhibition of different viruses, namely hepatitis B virus (HBV) (Lu *et al*., 2008a), influenza virus (Mehrbod *et al*., 2009; Xiang *et al*., 2011), human para-influenza virus type 3 (HPIV-3)

(Gaikwad *et al*., 2013), Herpes simplex virus type 1 and 2 (HSV-1 and HSV-2) (Sun and SteveaLin 2005), Coxsackie virus B3 (Ben Salem *et al*., 2012), tacaribe virus (TCRV) (Speshock; Murdock 2010), Vaccinia virus (Trefry and Wooley 2013)and monkey pox virus (MPV) (Rogers *et al*., 2008). Naked AgNPs have no risk of cell toxicity and have strong antiviral activity providing a robust protection against influenza virus infections (Mehrbod; Motamed 2009; Xiang; Chen 2011). Different stabilizing agents like polyvinylpyrrolidone, citrate and polyethylene glycol, added to AgNPs have also been proven to be biologically compatible and reduce infectivity; however, they may render the AgNPs less efficacious. In fact, a polysaccharide coating shields the cell from the lethal effects of the AgNPs, but it also decreases its activity against TCRV (Speshock; Murdock 2010). Indeed, the same capping agent proved to be very efficacious against MPV, where polysaccharide-coated AgNPs of 10 nm were highly effective in reducing MPV-prompted plaque formation *In vitro* (Rogers; Parkinson 2008).

Other examples of coated AgNPs are offered in several studies having as antiviral target human immunodeficiency virus type-1 (HIV-1) (Lara *et al*., 2011; Sun & Stevea Lin, 2005), HSV and respiratory syncytial virus (RSV) (Sun *et al*., 2008). AgNPs with a surface coating of poly (N-vinyl-2-pyrrolidone) (PVP) within the range of 1–10 nm proved to be the most efficacious nanoparticles to inhibit replication of HIV in a dose dependent manner (Elechiguerra *et al*., 2005). AgNPs were able to inhibit a large number of HIV-1 isolates comprising experimental strains, clinical strains, resistant strains, macrophage [M] and T lymphocyte [T] tropical strains, suggesting they may be broad band anti-HIV-1 agents (Lara; Ayala-Nunez 2010). In fact, PVP-coated AgNPs have been tested as a topical vaginal microbicide endowed with virucidal activity to prevent transmission of HIV-1 infection (Lara; Ixtepan-Turrent 2011)or as coating for polyurethane condoms to directly inactivate infectious microorganisms (Fayaz; Ao 2012). Both studies proved to sensibly inactivate HIV infectivity. The precise mechanism of action is not completely understood, but numerous data is available which points to a direct interaction of AgNPs with surface glycoproteins and interference with binding and fusion events of viral infiltration into vulnerable cells. Furthermore, AgNPs are able to obstruct post-entry stages of the HIV-1 life cycle by exploiting their ability of direct binding with RNA or DNA molecules (Sun; Singh 2008). The exploitation of AgNPs as antivirals is still in its infancy, and advance studies are necessary to illuminate the mechanism of action, which may reduce possible antiviral development of AgNPs to fill the vital niche of a broad spectrum antiviral agent.

Anticancerous activity of AgNPs: Early diagnosis to any disease condition is vivacious to make sure that early treatment is started resulting in a better chance of cure and this is predominantly true for cancer (Coulter *et al*., 2013). One important point in the effectiveness of anticancerous drugs is related to the possibility of reaching the target site in sufficient concentration and to the proficient activity without causing damage to neighboring healthy tissues and cells (Misra *et al*., 2010; Seigneuric *et al*., 2010). In this direction, nanotechnology represents, one of the new technologies with possibility to enhance the diagnosis and treatment of cancer (Dos-Santos *et al*., 2014). This could be achieved by developing unique imaging agents, multiple functional target devices capable of avoiding obstructions to supply therapeutic agents directly to the biological targets involved in cancer, along with nano-biosensors for predicting the disease and minimizing the growth of cancer cells and reducing the cost of treatments (Jain 2010; Qiao *et al*., 2010; Rai; Kon 2014). Metallic nanoparticles, in this area, appear as important agents, since they are used in several biomedical applications, such as highly sensitive diagnostic assays and biosensors (Rai & Ingle, 2012), thermal, and radiotherapy enhancement (Qiao; Wang 2010), as well as drug and gene delivery with relatively low toxicity (Bhattacharyya *et al*., 2012; Conde *et al*., 2012). It is known that AgNPs show complex interaction with intracellular cells and biomolecules like carbohydrates, proteins, lipids, DNA and RNA; probably through ROS, resulting in the death of apoptotic bodies and necrotic cells due to the cytotoxicity of biogenic AgNPs. Although all of these possibilities are still under studies to find out the precise mechanism (Duran *et al*., 2010; Jeyaraj; Rajesh, 2013).

To target epidermal growth factor receptor (GFR), a nano-composite particle comprising multiple functional magnetic silver working with cetuximab and a monoclonal antibody was designed by Zhao *et al*. (2012). GFR is a striking target of many types of cancerous cells, strongly concomitant with tumor metastasis, reappearance, and reduced overall persistence (Pan *et al*., 2008). Depending upon their size and concentration, AgNPs are used as good sensitizers for the cure of radio resistant glioblastoma malignant tumor (Xu *et al*., 2009). Sensitizing capability of AgNPs was further enhanced by using higher concentrations and increasing the surface area to volume ratio of nanoparticles by selecting smaller sized particles. The mechanism of sensitization was assumed to be dependent on the discharge of silver ion, which afterwards captured the free electrons resulting in the generation of an oxidative agent. Additionally, it also reduced the production of ATP and increased the synthesis of ROS (Asharani *et al*., 2009a; Asharani *et al*., 2009b). The toxicity of AgNPs is inclined by several factors, such as concentration, time, dose and size of the particles. Against MCF-7 cell culture, it was found that toxicity is dose-dependent and causes cellular damage in Human Epidermoid Larynx (Hep-2) cell line through ROS formation (Jacob *et al*., 2012). Biologically synthesized AgNPs from the leaf of *Suaeda monoica* on Hep-2 cells exhibited dose-dependent toxicity (Satyavani *et al*., 2012). AgNPs biogenically synthesized from *Podophyllum hexandrum* leaf extract showed a cytotoxicity and apoptotic effect, probably through caspace-cascade activation and loses of mitochondrial integrity (Jeyaraj; Rajesh 2013).

Cheng *et al*. (2013) described the production of AgNPs conjugated with fluorescent nano-diamonds for cell labeling and photo-dermal therapy (PDT). Furthermore, the authors also revealed that this multiple functional nano-material was non-cytotoxic, easy to produce and could be effectively used in photo-thermal therapy (PTT) against various tumor cell lines(Cheng *et al*., 2013). In a recent study, biogenic AgNPs from *Vitex negundo* leaf extract showed inhibition of proliferation of human colon cancer cell line HCT15. These results show that AgNPs may exert anti-proliferative effects on colon cancer cell line by overwhelming its growth, arresting growth phase, decreasing DNA synthesis and prompting apoptosis (Prabhu *et al*., 2013). Tse *et al*. (2011) offered an innovative technique to selectively abolish cancer cells. In their study, they used floated silver (dendrimer composite) nano-devices to destroy human epidermoid cancer cell line, resulting in the sub-sequential smashing of the labelled cancer cells by the micro-bubbles produced due to increased endorsement of laser light energy via AgNPs(Tse *et al*., 2011). Wang *et al.* (2013) studied the effect of AgNPs on rat glioma C6 cells combined with hyperthermia treatment and revealed that AgNPs (15nm) can prompt apoptosis and boost up radio sensitivity on cancer cells. The examination of hematologic parameters showed that AgNPs are effective in reducing white blood cell and platelet counts in tumour bearing mice as compared to controls(Wang *et al*., 2013). This was verified recently by De-Lima *et al*. (2012, 2013) in cytotoxic and genotoxic biogenic AgNPs studies (De-Lima *et al*., 2013; De-Lima *et al*., 2012). Recently, *In vitro* cytotoxicity of the AgNPs against breast cancer cell line (MCF-7) was studied by Ranjitham *et al*. (2013). The AgNPs showed significant cytotoxicity against the MCF-7 cell line at different concentrations (50, 100, and 150 mg) and also reported that the toxicity increases with increase in concentration of AgNPs (150 mg). The result suggested that the proliferation of MCF-7 cells was considerably inhibited by using higher concentration of AgNPs (Ranjitham *et al*., 2013).

Anti-inflammatory effects of AgNPs: In recent times, there is a crucial need to work out for the innovation and development of new anti-inflammatory medications due to increased frequency of inflammatory diseases which are typically non-responding to the already existing drugs. There are many challenges for the development and commercialization of safe and proficient anti-inflammatory drugs (Ravindran *et al*., 2013). In several studies described previously, the anti-inflammatory activity of AgNPs has been reported (Ajuebor *et al*., 1999; Bhol and Schechter 2007; Fiorentino *et al*., 1991; Paquet and Pierard 1996). Nadworny *et al*. (2008) applied 1, 2-dinitrochlorobenzene (DNB) topically to prompt contact dermatitis in swine in order to assess the anti-inflammatory properties of AgNPs. Wound dressings soaked in AgNPs and $AgNO_3$ solutions were used for the cure of resultant contact dermatitis and histopathological analysis showed near-normal pig epidermis after 72 h of treatment with AgNPs, leading to the inference that AgNPs have anti-inflammatory effects(Nadworny *et al*., 2008). Anti-inflammatory action of AgNPs might be interceded by decreasing cytokine release (Castillo *et al*., 2008), reducing mast cell and lymphocyte infiltration (Boucher *et al*., 2008)and prompting apoptosis in inflammatory cells (Nadworny; Wang 2008; Wright *et al*., 2002). Wong *et al*. (2009) reported that AgNPs had anti-inflammatory properties, in peritoneal adhesion model in addition to the burn wound model in mice. Considerably lesser concentration of the pro-inflammatory cytokine (IL-6) was found in the burn model mice that was treated with AgNPs by means of quantitative real-time polymerase chain reaction (PCR)(Wong *et al*., 2009). On the other hand, mRNA levels of an anti-inflammatory cytokine (IL-10) remained higher in the AgNPs treated mice group in contrast with other silver compounds ($AgNO_3$ and AgCl) at all recorded-points observed during healing process (Tian *et al*., 2007). An optimal dose of AgNPs (100 um) induced heat shock protein (Hsp70) over expression and provides an anti-inflammatory effect in Clone 9 cells(Ho *et al*., 2013). Matrix metalloproteinases (MMPs) are believed to induce inflammatory processes and tissue damage. Their over-expression result in chronic ulcers instead of acute wounds, leading to an assumption that the MMPs are involved in the non-healing nature of chronic ulcers. Porcine model was used to investigate the anti-inflammatory effect of AgNPs dressings which considerably decreases the MMP-9 levels resulting in better wound healing in shorter time (Wright; Lam 2002). In a human clinical study, AgNPs dressings stimulated curing process of stalled chronic leg ulcers (Sibbald *et al*., 2007). A decrease in neutrophil infiltration during biopsy revealed the anti-inflammatory activity of AgNPs which might be attained by decreasing the strength of pathogenic bacteria in the wound. From all these studies we conclude that AgNPs have strong anti-inflammatory activity and upgraded the healing processes as compared to conventional dressings.

Use of AgNPs in diagnosis and imaging: Nanotechnology has encouraged scientists to develop innovative and upgraded nanomaterials to provide enhanced biomolecular diagnosis, imaging and therapy. AgNPs are renowned for their unique and amazing optical properties (intense color and high scattering of light) which originate due to localized surface plasmon resonance (SPR), i.e. the combined oscillations of free electrons at a metal dielectric interface when the frequency of incident light overlaps with the frequency of electron oscillation. These optical properties of AgNPs depend on various parameters such as their shape, size, composition and environment along with the three-dimensional (3D) arrangement of particles. The size-dependent absorbance of AgNPs was studied to reveal how the size and composition of nanoparticles can be employed to modify the optoelectronic properties (Krutyakov *et al*., 2008; Mock *et al*., 2002). According to the report of Nie & Emory (1997), for a given excitation wavelength, AgNPs of different sizes and shapes displayed enhancement signals in the region of 10^{14} to 10^{15}. These enhancement signal properties were standardized and the results sturdily recommend the idea that size-dependent localized SPR subsidizes to surface

enhanced Raman signals strong enough to perceive even single molecules (Ravindran; Chandran 2013).

In recent times, identification of several biomolecular analytes by means of newly developed plasmonic sensors have grabbed the attention of the researchers. The plasmonic properties of AgNPs contribute to the large intensities observed in surface enhanced Raman spectroscopy (SERS). By using SERS, the Raman signal of a biomolecular analyte can be significantly intensified by adsorbing it onto hot-spot areas of the AgNPs such as gaps and intersections, leading to an increase in signal which is strong enough to allow even a single biomolecule detection (Potara *et al*., 2012). Owing to its capability of million fold enhancements in Raman scattering, AgNPs emerge as an extremely profound tool for not only trace analysis but also for probing single biomolecules(Ravindran; Chandran 2013). In the meantime, the current antibody based techniques cannot be used for the detection of virus particles present in low levels due to their lack of sensitivity in contrast to SERS which has arisen as a powerful tool and widens its potentials in vibrational spectroscopy. A study was carried out by Huang *et al*., (2008), in which the authors determined Raman spectra of Respiratory Syncytial Virus (RSV) by using SERS and silver nano-rods as substrate(Huang *et al*., 2008). The outstanding biosensing properties of AgNPs are progressively exploited by different researchers (Schultz *et al*., 2000; Shrivas and Wu 2008). Conjugation of AgNPs to proteins has incredible applications in imaging, biosensing, catalysis, therapy, drug delivery, and regulator of protein assembly and activity(Austin *et al*., 2014).Walkey *et al.,* (2011) studied the interaction of serum albumins with AgNPs demonstrating a two-fold increase in hysteresis effect due to exposure of aggregated AgNPs and the conformational alteration of serum albumins, suggesting that this hysteresis theory might be useful in the bio-detection and bio-analysis applications of AgNPs. However, to understand the mechanism involved in the functionalization of AgNPs with nucleic acids (DNA and RNA), amino acids and proteins still requires an intensive study(Walkey *et al*., 2011).

Use of AgNPs in implanted devices and catheters: Implantable devices and catheters are of primary risk factors involved in acquiring of hospital-associated infections during medical intercessions. Implantable devices are categorized into two main classes; devices that are wholly embedded inside the patient and devices implanted partly inside the body that are exposed to the outer environment. Entirely embedded devices can be contaminated in the course of implantation and necessitate prophylactic anti-toxin treatment, for example, heart valves for the initial couple of days after operation to maintain a strategic distance from contamination (Califf *et al*., 2004; Lee *et al*., 2014). On the other side, devices that are partially implanted within the body, for example, urinary and venous catheters are defenseless against bacterial colonization because of non-stop introduction to the exterior environment. The increased risk of contamination confines the utilization of such implanted devices and catheters in medical practice (Stevens *et al*., 2009). Grunkemeier *et al.* (2006) designed a prosthetic silicone heart valve (Silzone) covered with elemental silver to diminish the recurrence of endocarditis emulating valve substitution and was progressively utilized as a part of a medical experimentation. The logic behind the utilization of elemental silver was to restrain bacterial colonization occurring on the silicone valve, consequently minimizing the risk of inflammation of heart(Grunkemeier *et al*., 2006). Broad study has been carried out on the lethality testing of the silver heart valves demonstrating them a promising biocompatible device in implantation (Jamieson *et al*., 2009). A novel nano-composite material has been synthesized by Andara *et al.,* (2006), based on carbon (diamond) embedded with 4 nm AgNPs in the matrix and was explored for hemo-compatibility properties when utilized as a surface coating for cardiac medical devices such as stents and heart valves. Platelet adhesion studies revealed reduced platelet sticking with the surface of the nano-composite demonstrating that the material has anti-thrombogenic properties. The authors also presumed that the nano-composite material embedded with AgNPs have antibacterial properties, yet no data was given to support this statement (Andara *et al*., 2006; Ghanbari *et al*., 2009). Urinary tract diseases constitute an extensive extent of nosocomial contaminations, and the urinary catheter is the most critical inclining factor (Meenakumari *et al*., 2013). A micron-scale coating based on AgNP-Polydopamine (PDA)bilayers combined with poly (sulfobetaine methacrylate-co-acrylamide), showing anti-biofilm and anti-crust properties was effectively created for silicone urinary catheters by Wang *et al*. (2014).The coating method expanded the catheter surface lubricity yet did not altogether change the mechanical property of the catheters, and the altered catheters can decrease bacterial attachment and biofilm formation by approximately two orders of magnitude(Wang *et al*., 2014).

Central venous catheters (CVC) are widely utilized as a part of clinical practice, with around five million being implanted in the United States alone every year (Mermel 2000). Previous studies proposed that the impregnation of catheters with antibiotics can reduce the rates of colonization of catheters(Sheng *et al*., 2000). Even so, there is a hazard that the growing use of antibiotic impregnated catheters can prompt extreme bacterial resistance. Several different methodologies have been used to explore the antibacterial activity of silver-impregnated polymers to inhibit biofilm growth on the surface of catheters(Samuel and Guggenbichler 2004). Most frequently used polyurethanes, at present recognized as plastic catheters, have been altered with nano-silver. To form effective antibacterial catheters, plastic catheter tubes can be promptly covered with a thin layer of nano-silver. Roe *et al*. (2008) affirmed that the nano-silver catheter was non-hazardous by performing a 10-day *In vivo* study in mice. Silver-impregnated catheters in which silver ions are fortified with an inactive porcelain zeolite, has now gotten to be open for medical use(Roe; Karandikar 2008). To check the frequency of catheter-related blood stream infections, Khare *et al.,* (2007) compare silver-impregnated catheters with ordinary catheters and reported that the inclusive colonization level was considerably lower in the

silver impregnated CVC signifying its role in clinical practices(Khare *et al*., 2007).

Catheters are also utilized as a part of neurosurgery to drain extra cerebrospinal liquid (CSF), which can result in cerebral hypertension and brain damage. Neurosurgical catheters can be wholly implanted and work as shunts to distract CSF permanently, or can be momentarily utilized as external drainage devices(Bayston *et al*., 2007). Both of these applications are liable to bacterial infection, which can quickly spread to the brain and the nearby tissues(Orsi *et al*., 2006). AgNPs are emerging as a powerful tool in day-to-day neurosurgical practices, because of its excellent antibacterial properties and less noxiousness. Neurosurgical catheters have been fabricated by impregnation with nano-silver to reduce catheter-related infections(Galiano *et al*., 2008). External ventricular drainage (EVD) placement for momentary CSF distraction is a common therapeutic technique. A retrospective study of 403 patients with a total of 529 implanted EVDs catheter (plain polyurethane vs. silver-impregnated) was carried out by Lajcak *et al*. (2013). This report provides relative information on EVD infections as to the kind of catheter. Silver-impregnated catheters displayed considerably lower infection rates in contrast to non-impregnated catheters(Lajcak *et al*., 2013). External ventricular drain catheters impregnated with nano-silver were utilized to figure out whether nano-silver is helpful in avoiding catheter-associated ventriculitis (CAV) or not by Lackner *et al*. (2008). Nineteen patients with acute occlusive hydrocephalus received the nano-silver catheter and were evaluated reflectively against a control group that received ordinary catheters. Results showed that in the control group, out of twenty, five were positive for CAV while in the group with nano-silver catheters, all CSF cultures were negative and there were no cases of CAV, suggesting that the nano-silver is potentially useful in the stoppage of CAV and is encouraging for *In vivo* use in humans. However, extensive randomized clinical trials are necessary to further authenticate this pilot study(Lackner *et al*., 2008).

Use of AgNPs in wound dressing and healing: Wound healing is considered as an intricate and several step procedure which involves integration of different activities of various tissues and cell lines (Martin 1997). Currently, AgNPs wound dressings have become available commercially (Acticoat^{TM}) and are being used in modern medical practices for the treatment of several wounds, comprising burns (Chen *et al*., 2006; Huang *et al*., 2007b; Vlachou *et al*., 2007), Steven–Johnson syndrome(Yang *et al*., 2007), toxic epidermal necrolysis (Asz *et al*., 2006), chronic ulcers(Sibbald; Contreras-Ruiz 2007) and pemphigus(Yang; Huang 2007). Besides burn wounds treatment, presently there is a growing demand for the utilization of AgNPs in the treatment of chronic wounds, for example, diabetic foot and leg ulcers(Gravante *et al*., 2009). Ambrogi *et al*., (2014) prepared novel chitosan films comprising mesoporous SBA-15 supported AgNPs which were applied as an efficient wound dressing material. These chitosan films containing AgNPs displayed excellent hydration properties, mechanical properties and better water vapor transmission rate. After hydration, these AgNPs supported chitosan films demonstrated excellent antimicrobial activity against both Gram positive (*Staphylococcus epidermidis* and *Staphylococcus aureus*) and Gram negative (*Pseudomonas aeruginosa*) bacteria(Ambrogi *et al*., 2014).

Various silver products and AgNPs wound dressings have a positive effect on wound healing and often used to prepare the wound for healing and to maintain a microbe free environment for wound healing (Warriner and Burrell 2005). For the treatment of burns, randomized clinical trials demonstrated the outstanding wound healing properties of AgNPs dressings as compared to other available gauze and silver sulfadiazine dressings. One Randomized clinical trial verified the effectiveness of AgNPs dressing in competition with conventional silver sulfadiazine dressing by using a control group and 98 patients with 166 different burn wounds. AgNPs dressings considerably enhanced bacterial leeway from infected wounds and essentially diminished wound recovering time by an average of 3.35 days without any adverse effects(Huang; Li 2007b). Abdelgawad *et al.* (2014) conducted a prospective study for the evaluation of antibacterial properties of AgNPs dressing on a wide range of chronic non-healing wounds. They reported that the use of AgNPs dressings as compared to other silver compounds is beneficial for the protection of wounds from bacterial infection(Abdelgawad *et al*., 2014). Liu *et al*. (2010) reported that AgNPs can exert sound effects on keratinocytes and fibroblasts during healing process and indorse wound healing through encouraging the propagation and relocation of keratinocyte(Liu *et al*., 2010).

In a study, chitosan based AgNPs wound dressings exhibited superior healing rates (89%) as compared to chitosan film (74%) and silver sulfadiazine dressings (68%). Moreover, the chitosan based AgNPs dressings deposit less silver on wounds than silver sulfadiazine dressings, thus validating the safer use of AgNPs in wound healing and decreasing the rate of recurrence of argyria (skin discoloration) and argyremia (elevated silver concentration in blood) (Lu *et al*., 2008b). Habiboallah *et al*. (2014) design AgNPs periodontal dressing to evaluate its effects on gingival wound healing by using animal model (Thirty healthy adolescent female rabbits) having unbroken teeth. The radiographic and clinical investigation exposed no periodontal disease. Gingivectomy was performed at the buccal gingiva of the left and right mandibular incisors and subsequently, untreated wounds in the control area were covered with periodontal pack (control) and periodontal dressings were applied in the test regions. Histological variations were examined in day 4 and 7 post operation and the authors detected remarkable difference in the inflammatory and repair parameters of the healing process between surgical sites treated with this periodontal dressing and control group. Besides, wounds treated with silver NPs dressing in general terms had all the hallmarks of relatively complete healing one week post operatively (Habiboallah *et al*., 2014). The utilization of AgNPs is being embraced by pharmaceutical to give better treatment to an extensive range of wounds and for enhanced treatment of burns (Ambrogi; Donnadio 2014).

Use of AgNPs in artificial orthopedic implants: Bone cement has been used efficaciously to anchor artificial joints and fractured bones in orthopedic surgeries for more than half a century. This type of surgery consists of the substitution of an impaired body parts resulted either by a degenerative disease or by a severe injury with an artificial/manufactured one. The basic sorts of operations are knees, hip and spine disk substitution with artificial one(Prokopovich *et al*., 2013). The customary methodology used to inhibit infections triggered by the implantation of bone cement is through the utilization of antibiotics either via parental delivery (Meehan; Jamali 2009; Tyllianakis *et al*., 2010)or via discharge from the bone cement itself (Kaplan *et al*., 2012; Kittinger *et al*., 2011; Nowinski *et al*., 2012; Ofluoglu *et al*., 2012; Van de Belt *et al*., 2001). Though, the dependence on antibiotic treatments seems, by all accounts, to be a time-restricted solution due to the persistent intensification of micro-organisms resistance to these particles (Montanaro *et al*., 2011; Zilberberg and Shorr 2013). Therefore, the advancement in the field of antimicrobial treatments or prophylactic therapies not grounded on antibiotics is of specific interest and immensely vital. The use of nano-metals, predominantly silver(Pathak and Gopal 2012) is an encouraging example of such alternate methodologies. Nanocomposites and nanomaterials such as AgNPs, nanofibers, nanoscaffolds, nanocoatings and nanosurfaces are used in several applications in orthopedics and traumatology (Morley *et al*., 2007; Xie *et al*., 2014).

Alt *et al.* (2004) used AgNPs as an antimicrobial additive to polymethyl methacrylate (PMMA) bone cement, suggesting AgNPs as a mean to decline the rate of resistance through its multi-dimensional mechanism of actions. Furthermore, displaying an impressive *In vitro* potent antibacterial action against methicillin-resistant *S. epidermidis* and *S. aureus,* low cytotoxicity and inhibition of biofilm growth(Alt *et al*., 2004). AgNPs were synthesized under different conditions by using tiopronin as capping agent and antimicrobial activity of bone cement comprising these tiopronin capped AgNPs in different ratios was then evaluated against *Staphylococcus aureus* (methicillin resistant) by Prokopovich *et al*., (2013). This study revealed that the AgNPs larger in size with a higher concentration of silver were more dynamic in antimicrobial action than the smaller ones which had more prominent amount of tiopronin (Prokopovich; Leech 2013). Prokopovich (2014) encapsulated oleic acid capped AgNPs with bone cement based on PMMA samples at different ratios and assessed the antimicrobial activity of AgNPs at concentrations as low as 0.05% (w/w) against *Staphylococcus aureus* (methicillin resistant), *Acinetobacter baumannii*, *Staphylococcus aureus* and *Staphylococcus epidermidis*. Moreover, the authors studied the cytotoxicity and mechanical properties of the bone cement containing these AgNPs, suggesting that such materials are innocuous to be used in orthopedic surgery (Prokopovich 2014). Xie *et al*. (2014) used hydroxyapatite coatings integrated with different growth factors and AgNPs on metallic implant surfaces for improvement of osteoinductivity and antimicrobial properties. The *In vivo* and *In vitro* studies indicate that these coatings have good osteoinductivity properties offerings an advantageous and efficient method for the integration of AgNPs and growth factors into calcium phosphate coatings (Xie; Lu 2014). As a result, it seems that AgNPs could play a momentous role in the up-coming generation of biomaterials in orthopedics.

Impact of AgNPs on human health and environment: The wide-ranging antimicrobial properties of AgNPs boost up its applications in various fields such as biomedical, water and air purification (De-Gusseme; Sintubin 2010; Sheng and Liu 2011), food production (Gottesman *et al*., 2011), cosmetics (Kędziora *et al*., 2013), clothing (Freeman *et al*., 2012), and numerous household products(Prabhu and Poulose 2012). By the rapid progress in nanotechnology, applications have been technologically advanced in diverse fields of life and now silver (in different forms) is the engineered nanomaterial most frequently utilized as a part of consumers items (Kędziora; Gorzelanczyk 2013; Rejeski 2009). Given the immense number of consumer products describing the benefits of AgNPs, it seems judicious to evaluate the impending human and ecological deathtraps linked with its enlarged manipulation. The more widespread use of AgNPs becomes the potential threat for human and ecosystem and therefore, concerns regarding the toxicity and environmental impact of AgNPs have become prevalent (McAuley *et al*., 2014). At the point of production, AgNPs may be discharged to the environment from wastes, corrosion of nanomaterials used in domestic life such as silver coated antibacterial water filter, and from washing or dumping of silver-containing items (Benn & Westerhoff 2008). Release of silver to both natural and designed frameworks will probably impact the lower trophic levels initially, i.e., bacteria. However, there is a poor knowledge about trophic exchange of silver in environment and its adversarial effects on humans. It is calculated that tones of silver are discharged from industrial wastes into the environment, and the toxicity of silver is mainly due to release of free silver ions in the watery phase (Panyala *et al*., 2008).

The main routes of exposure of AgNPs to human body would be the skin, respiratory and gastrointestinal systems, which are the crossing point between the interior framework of the human body and the outer environment (Arora *et al*., 2012; Chen and Schluesener 2008). Currently, scientists are giving extraordinary attention to study the toxicological aspects of the nanoparticles before preceding to their applications. Recently, both *In vitro* and *In vivo* models are being exploited for studying the toxicological aspects of the nanoparticles. One of those studies comprise, intravenous administration of AgNPs (20–100 nm) to rats to evaluate its toxicological effects. The AgNPs administration resulted in the severe increase of spleen size as well as an increase in T and B cells population. Amassing of AgNPs in spleen, lymph nodes, liver and other organs of the affected tissues was shown by the histopathological study. The clinical analysis showed an increase in phosphatase, aspartate transaminase and alanine transaminase levels, which all indicated the liver damage in rats (De-Jong *et al*., 2013).

As indicated by a study performed by Trop *et al*. (2006), AgNPs can come into the body via ingestion and enter the portal vein after absorption from the stomach. Well ahead, AgNPs enter the liver via portal vein and therefore exerting the noxious effect on liver and allied cells (Trop *et al*., 2006). To investigate the particulars of liver impairment due to toxicity of AgNPs, Hussain *et al*. (2006) and Xia *et al*. (2006) have performed an experiment on liver cells of mouse. The authors witnessed the abnormal increase in size of mitochondria in the bare liver cells besides the uneven cell shape and their unusual cleavage due to the action of AgNPs. The organ with extraordinary high metabolic activity is the liver, where excessive accumulation of AgNPs takes place resulting in the liver damaging(Hussain *et al*., 2006).

Ramirez-Lee *et al*., (2014) have assessed the toxic effects of AgNPs on smooth muscle cells that are of prime importance in our body controlling the airway contractility by involving different intermediary such as acetylcholine and nitric oxide. On exposure to smooth muscle cells, AgNPs cause the initiation of acetylcholine reliant cytotoxicity even at low concentration of 10 and 100 g/mL and also decrease cellular propagation intervened by muscarinic receptor-tempted nitric oxide synthase pathway. The excessive production of nitric oxide is the outcome of AgNPs cytotoxicity(Ramirez-Lee *et al*., 2014). Lee *et al*., (2010) have reported AgNPs exposure results in modulation of the expression of several genes linked with motor neuron disorders, neurodegenerative disease, and immune cell function, representing potential neurotoxicity and immune toxicity (Lee *et al*., 2010). Stebounova *et al*., (2011) also reported slight pulmonary inflammation of mice right after 10 days of AgNPs exposure(Stebounova *et al*., 2011). Kim *et al.* (2008) studied the gastrointestinal toxicology caused by AgNPs exposure via ingestion and have tested the oral toxicity of AgNPs ranging in size from 50-60 nm over a time of 28 days in Sprague-Dawley rats. Results revealed that the male and female rats did not express any noteworthy changes in body weight but some major changes were observed in the basic alkaline phosphatase and cholesterol levels indicating that exposure to over more than 300 mg of AgNPs may lead to liver damage. It was proposed from this study that AgNPs do not encourage genetic cytotoxicity in female and male rat bone marrow (Kim; Kim 2008). However, few reports are available regarding the studies on toxicity of AgNPs via skin exposure or injection to organism (Rahman *et al*., 2009; Samberg *et al*., 2010).

Asharani *et al*., (2009a) studied the toxicity of starch-coated AgNPs on normal human lung fibroblast cells (IMR-90) and human glioblastoma cells (U251), by observing alterations in cell physiology and morphology, metabolic activity, and cell viability. Authors proposed a probable mechanism of toxicity of AgNPs which involves the distraction of mitochondrial respiratory chain, resulting in formation of ROS and stoppage of ATP production, which sequentially leads to DNA destruction(Asharani; Low Kah Mun 2009b). In testicular cells, the cytotoxic and genotoxic effects of metallic nanoparticles including AgNPs (20 nm), titanium dioxide nanoparticles (TiO_2NPs; 21 nm), and submicron (less than 200 nm) have been studied by Asare *et al*. (2012). The result showed that submicron particles and AgNPs are more genotoxic and cytotoxic in contrast to TiO_2NPs resulting in necrosis and apoptosis(Asare *et al*., 2012). In a recent study, the impact of different concentrations of AgNPs on human mononuclear cells was investigated by Barkhordari *et al.* (2014) to study the cytotoxicity of AgNPs. In this study, AgNPs (10 nm) in various concentrations ranging from 1–500 μg/mL were incubated with blood mononuclear cell suspensions taken from ten healthy young men for 6 and 24 hours by MTT (3-[4, 5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, a yellow tetrazole) assay. For comparison positive and negative controls were also used. Results revealed that 10.9% to 48.4% of the mononuclear cells were died after 6 hours of contact with AgNPs. The percentage of mononuclear cells death ranged from 56.8% to 86.3% after 24 hours of contact with AgNPs. By this experiment, it was concluded that by increasing the contact time with AgNPs from 6 to 24 hours, there was a considerable increase in the cytotoxic effects of AgNPs at all concentrations used (Barkhordari *et al*., 2014).

As the products containing AgNPs are extensively used in daily life, the release of AgNPs and silver (in the form of $AgNO_3$, AgCl and free silver ions) into the environment becomes a burning issue. There are numerous reports regarding silver discharge into environment from diverse materials comprising textiles(Benn and Westerhoff 2008; Geranio *et al*., 2009; Reidy *et al*., 2013), paints (Kaegi *et al*., 2010), disinfecting sprays (Blaser *et al*., 2008; Gottschalk *et al*., 2009; O'Brien and Cummins 2010; Walser *et al*., 2011), deodorants and cosmetics (Wijnhoven *et al*., 2009). A study relating to the discharge of silver from textiles was conducted by Geranio *et al.* (2009). The authors studied nine different fabrics and suggested that the quantity and form of silver discharged into the environment intensely rely on the approach through which the silver is integrated into a fabric(Geranio; Heuberger 2009). Release of nanosilver from outdoor paint was explored by Kaegi *et al*. (2010) by performing an experiment that was conducted over 372 days. They found noteworthy leaching of AgNPs (145 μg Ag/L) in contrast to the titanium pigments that were released only about 1% during one year(Kaegi; Sinnet 2010). Further investigation exposed that maximum amount of discharged silver was transmuted into less dangerous forms, for example, Ag_2S and released AgNPs were generally less than 15 nm in size. Inclusive use of outdoor paints containing silver can thus add a momentous increase in the quantity of silver discharged into the environment as most of the AgNPs from the outdoor paint were moved out after one year. Despite significant release of silver from outside paints, it is not considered in a number of the predominating models of silver fate in the environment (Blaser; Scheringer 2008).

There have been many reports on AgNPs describing the fact that they cannot differentiate between detrimental and beneficial bacterial strains and hence can lead to the destruction of many microbes beneficial to the ecology (Allsopp *et al*., 2007; Shoults-Wilson *et al*., 2011). Gottschalk *et al*., (2009) demonstrated environmental amassing concentrations of AgNPs and other different

nanoparticles for the U.S.A., Europe and Switzerland. Conferring to the outcomes, hazards to aquatic life developing from nanosilver structures can't be precluded in sewage treatment runoffs and in surface waters. In different environmental compartments, the calculated nanosilver concentrations were considerably lower than other types of nanomaterials, and these calculated nanosilver concentrations usually reflect the global production volumes(Gottschalk; Sonderer 2009). Threats to freshwater ecosystems developing from nanosilver integrated with textiles and plastics, continuously discharged into the environment were studied by Blaser *et al.,* (2008). In this study, every one of the 25 European Union countries were taken into records in determining the utilization of silver augmented materials and silver discharge into the environment. Conferring to the results, silver combined with plastics and textilesrepresents up to 15% of aggregate silver discharged into water systems in the Europe. The authors also proposed a hypothesis that only silver ions are discharged into the external environment instead of entire AgNPs, which is antagonistic to some existing data (Benn and Westerhoff 2008; Blaser; Scheringer 2008; Geranio; Heuberger 2009). Marine ecosystems were not considered at all in this study and discharges from construction processes, effluents from silver fused products and deposition from atmosphere to shallow water were also neglected. Silver release only from plastics and textiles were taken into consideration in this study, however, the current records inveterate the substantial release of silver from other sources also (Farkas *et al*., 2011; Kaegi; Sinnet 2010). Hence, it become mandatory to study more universal representations of silver fortune into the environment since the bulk of silver discharged into water is integrated into sewage mud (Kaegi *et al*., 2011) and then deposited on landfills or used as a fertilizer and thus results in soil and groundwater contamination.

Safety issues for the use of AgNPs concerning human and environment: Metallic nanoparticles in general and AgNPs in particular are the emergent causes of alarm for the human and environment administrators, because of the rising integration of AgNPs into consumer products. The extraordinarily powerful antimicrobial activity of AgNPs is a foremost direction in the advancement of nanosilver consumer products. Conferring to a market statistical surveying report, AgNPs are evolving as one of the speediest developing product categories in the nanotechnology business(Dos-Santos; Seckler 2014), including an extensive range of nanosilver products in medical field such as wound dressings, surgical instruments, contraceptive devices, and bone prostheses (Chen; Han 2006; Cohen *et al*., 2007; Muangman *et al*., 2006; Zhang *et al*., 2008; Khani and Ahmad, 2015). The "Project on Emerging Nanotechnologies (PEN) is dedicated to make sure that as nanotechnologies progress, possible hazards are diminished, public and purchaser assignation remains strong, and the possible prosperities of these novel technologies are recognized." AgNPs stand first among the most prevailing nanomaterial in end user products according to PEN (Dos-Santos; Seckler 2014). The massive use of AgNPs in the end user products, point out numerous inquiries in the mind of common individuals: Is it ok for me and my family? Is it true that it is non-hazardous for our environment? What may be the financial impact of nanotechnology on consumers and producer? To answer all these inquiries, investigations are needed to explore the fundamental physical and chemical attributes of nanoparticles that determine their hazardous potentials.

Release of AgNPs from the consumer products is expected to move in land-dwelling ecosystems, but their destiny and transformation is very complex, and very little is known about their impact on the environment. But due to extensive utilization of silver based products, the public is anxious about what will take place to different marine lives when AgNPs enter into water. Another anxiety about AgNPs is that they do not discriminate between beneficial and harmful microorganisms. Ma *et al*. (2014) reported that free silver or AgNPs present in municipal wastewater transformed considerably into Ag_2S during waste water treatment process. Detailed investigations about distribution, absorption, metabolism, and discharge of AgNPs is needed to recognize the fortune and noxiousness of AgNPs in the environment. With the growing use of engineered nanomaterials, it is likely to upsurge the occupational exposure to these nanomaterials in the workplaces. These nanomaterials may pass into our bodies and store there, possibly leading to the damage or death of humans. The investigations on the exposure assessments of AgNPs to human and ecosystems are just commencement steps. Thus, exposure evaluation focused around the ongoing checking of exposed nanoparticles is one of the critical issues for EHS (environment, health, and safety). As indicated by National Institute for Occupational Safety and Health, nanomaterial based items, for example, nanocomposites, surface-covered materials, and materials comprising nanostructures do not represent a danger of exposure during their usage. Yet, some of the practices used in their manufacture may prompt the exposure, for example, the cutting or hammering of such items could discharge respirable-sized nanoparticles (Handy *et al*., 2008). Engineered nanomaterials have complicated the safety issues and risk evaluations due to their innovative properties in contrast to bulk material, lack of information, non-uniformity and astonishing diversity (Klaine *et al*., 2008). The government organizations from distinctive republics in conjunction with researchers in the educated community, public, and private sectors are working collectively to reply above inquiries, assemble more information, and develop stratagems to counter the issues confronted for the risk estimation of the engineered nanoproduct. The environmental risk evaluation of nanoproduct could be accomplished by exploiting the existing approaches and monitoring framework, but with modifications to procedure encompassing their properties and characterization.

Conclusions and future perspectives: Nanotechnology speaks to a cutting edge and innovative approach to generate and test novel creations based on metallic nanoparticles with antimicrobial properties. AgNPs represent an eye-catching nanomaterial with potential application in the field of medicine and sanitation because

of their extraordinary physical and chemical attributes. Green synthesis of nanoparticles has upsurge in the field of nanotechnology to make unique materials that are ecofriendly, inexpensive and stable nanoparticles with an incredible vitality for extensive applications in every aspect of life. During the current scenario, nanotechnology motivates progress in all spheres of life, hence biosynthetic route of AgNPs synthesis will emerge as safer and best alternative to conventional methods. In spite of the fact that different biological entities have been used for the production of AgNPs, the use of plants for the facile robust synthesis of AgNPs is fabulous due to ease of accessibility, the non-hazardous nature, several choices available, and the benefit of faster synthesis over other methods. In green principle based methods, it was demonstrated by many reports that the AgNPs synthesized by plants are more stable in contrast with those produced by other biological entities. Plants (particularly plant extracts) have capability of reduction of silver ions in much shorter time as compared to fungi or bacteria. Moreover, in order to use easy and nontoxic green methods in scale-up and industrial production of AgNPs, plant extracts are unquestionably superior to plant biomass or living plants. Additionally, the plant extracts contains various biomolecules which act as reducing as well as capping agents so reducing the need of harsh solvents or surfactants for stabilization of AgNPs. Characteristics of AgNPs, for example, determination of size and shape are imperative not only for enhancing the antimicrobial activity, but also for decreasing tissue and eukaryotic cell toxicities. The applications of AgNPs are diverse and numerous, but the most exploited and preferred feature is their antimicrobial and anti-inflammatory activities. Many reports are available in the literature that emphasize on the antimicrobial effects of AgNPs against different pathogens comprising bacteria, virus and fungi. This marvelous property of AgNPs has been used in different practices in the medical field and henceforth has been exploited well. Although several mechanisms have been proposed in literature to attribute the fabulous antimicrobial activity of AgNPs, but the precise and most trustworthy mechanism is not fully understood or cannot be generalized as the AgNPs are reported to act in different ways on different microorganisms.

Currently, the flare-up of emerging and re-emerging contagious diseases has become a substantial burden on worldwide economies and public health. Broad-spectrum bioactivities of AgNPs make them promising agents not only in fighting infections but also in tackling serious problem of tumors and, particularly, multi-drug resistant cancer cells. AgNPs can be used in the diagnostics and treatment of different cancers. Many anti-cancer studies are in progress in *In vitro* assay and a few on *In vivo* studies. Therefore, this is an open area for many new studies in the cancer treatment with AgNPs. Currently, the applications of AgNPs have been increased in several areas such as drug delivery, molecular diagnosis and imaging, cure of vascular diseases, cancer therapy, wound curing and the development of novel medical devices such as catheters with antimicrobial properties. Conversely, the disadvantage of AgNPs is that they can prompt toxicity in eukaryotic cells and tissues at various degrees. It is recommended that higher concentrations of AgNPs are detrimental and can result in several human health issues. There are also many reports in literature emphasizing on the noxious effects of AgNPs to ecosystems causing many ecological problems if discharged into the environment. Thus, precautions must to be taken to use AgNPs in a good, compelling, and effective way, understanding its drawbacks and taking amazing care that it does not result in any damage to an individual or the environment. It can be expected that if AgNPs are used appropriately in a good way, they can be a worthy friend, but if used randomly, they can turn into a strong enemy. Henceforth, this current review closes with a belief and prayer to God that there would be systems developed to abolish any noxiousness produced by AgNPs to individuals and the environment so that the exceptional properties of this substance can be put to incredible utilization for human advancement without any disagreements.

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