IJPSR (2018), Volume 9, Issue 10 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 January, 2018; received in revised form, 27 April, 2018; accepted, 13 May, 2018; published 01 October, 2018

EMERGING USE OF GREEN SYNTHESIS SILVER NANOPARTICLE: AN UPDATED REVIEW

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Keywords:

Green synthesis
silver nanoparticle, Advantageous, Benefits, Problems to be overcome

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ABSTRACT: The aim of this review article is to reflect the current availed study on green synthesis of silver nanoparticle and its future prospects to treat chronic diseases. The development of eco-friendly and reliable techniques for synthesis of silver nanoparticles is a vital step in the area of nanotechnology. The researchers have shown more interest and attention on this because of its unique properties and applications in various fields such as medicine, catalysis, water treatment, nano electronics, pollution and textile field *etc*. This review is highlighting the advantages and benefits of green synthesis of silver nanoparticles over the other nanoparticles, using various plant extracts and it's applications in a specific cancer disease treatment as well as in other diseases. Green synthesis of silver nanoparticles with controlled release, drug targeting, as well as significantly increase the bioavailability of drugs, which greatly overcome the weaknesses of traditional drug delivery.

INTRODUCTION: Over the past few years, synthesis and characterization of nanoparticles has gained increasing momentum due to their large surface area to volume ratio because of which nanoparticles exhibit novel and new properties than their macroscopic counterparts. Thus, nano-technology has immense potential to revolutionize in the biomedical research by developing new and improved products for clinical diagnosis and therapy. Among nanoparticles, several noble metal nanoparticles such as silver, gold, copper and platinum were widely synthesized by employing various procedures including physical, chemical and biological methods.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.9(10).4029-55

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.9(10).4029-55

Silver nanoparticles have an eye catching role owing to their innumerable physical and chemical properties [1]. Silver nanoparticles are more potent than the silver ions as revealed in avant-garde research. The physical and chemical routes of nano-particles preparation have many dis-advantages and are not eco-friendly. Hence, researchers across the globe have searched for new and environmentally benign methods for the synthesis of biocompatible nanoparticles [2].

Incidentally, biological systems have long been known to reduce metal ions into nano-sized particles [3] and many researchers have recently reported the biogenic synthesis of silver and gold nano-particles using a wide range of biological resources like bacteria [4] fungi [5, 6] and plants [7, 8]. In the plant mediated green chemistry approach, the reduction rate of metal salts is very fast and the procedure itself requires no specific conditions unlike the physical and chemical methods [2, 9].

Besides, this biogenic method of nanoparticles synthesis appears to be reproducible and the particles, produced through this environmentally friendly approach, are found highly stable [10]. Hence, this one pot green chemistry procedure has attracted the attention of biologists and nanotechnologists in myriad ways and is recently emerged as one of the active areas of current nano biotechnological research. To date, as many as 1628 nano-based products as shown in **Fig. 1** are being extensively used for various purposes throughout the world [11]. Inorganic nanoparticles have already been utilized in wound healing and in antibacterial applications [12].

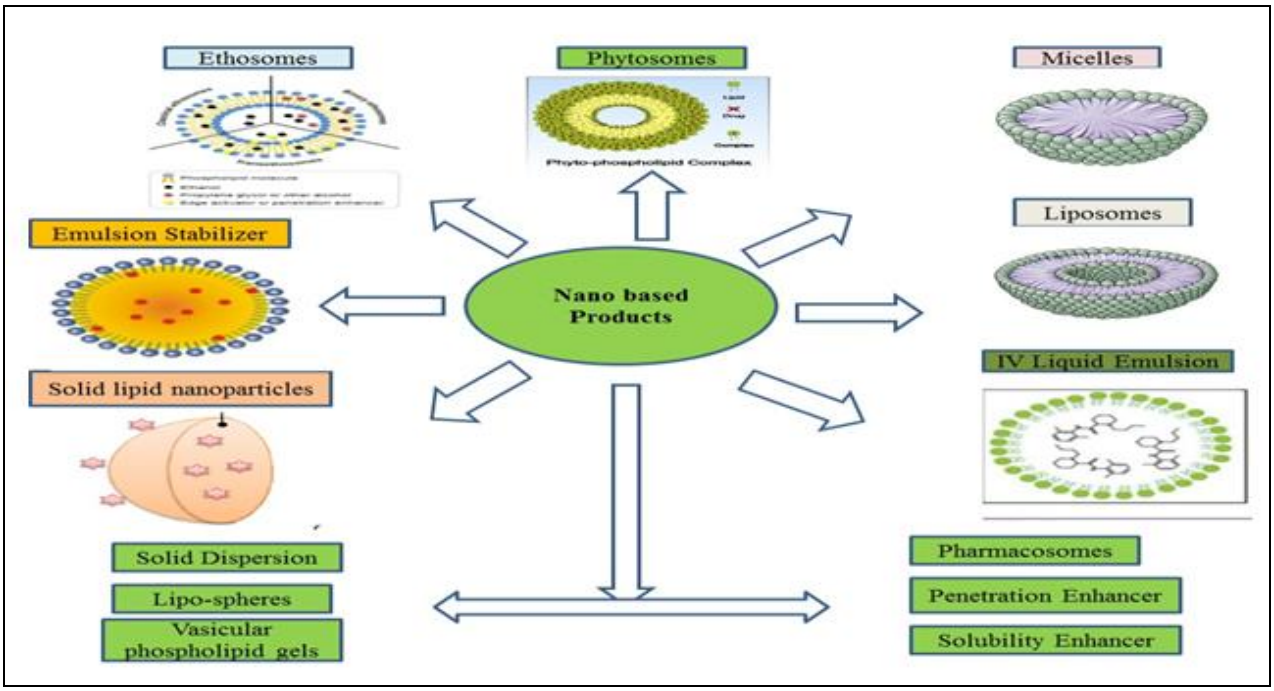

FIG. 1: NANO BASED PRODUCTS

Nano biotechnology, defined as biomedical applications of nano-sized systems, is a rapidly developing area within nanotechnology. Nanomaterials, which measure 1 - 1000 nm, allow unique interaction with biological systems at the molecular level. It is an upcoming field that could potentially make a major impact on human health [13]. It can also facilitate important advances in detection, diagnosis, and treatment of human cancers and have led to a new discipline of nano-oncology. Nanoparticles are being actively developed for tumour imaging *in-vivo*, bio-molecular profiling of cancer biomarkers, and targeted drug delivery.

These nanotechnology-based techniques can be applied widely in the management of different malignant diseases [14]. Silver nanoparticles (Ag-NPs) have been extensively studied for many decades due to their unique features and wide range of applications. Their uses include catalysis [15], bio-sensing [16], imaging [17] and antibacterial activity [18, 19].

Among these applications, antibacterial activities have gained much attention because they potentially offer a solution to the problem of antibiotic resistance [20]. There are a variety of methods to synthesize Ag-NPs including physical and chemical methods [21]. Chemical reduction of silver ions using sodium borohydride [22], hydrazine [23], ascorbic acid [24], trisodium citrate [25] and polyols [26] were reported and are considered well-established methods. Although chemical routes are effective, these methods may suffer from toxicity due to the chemicals used and the difficulty in removing them. Additionally, chemical reagents used in these methods are hazardous to the environment [27]. To avoid the toxicity of chemicals; green synthesis was developed [28]. This method of biosynthesis of metal nanoparticles has been proposed as a cost effective and environmental friendly way of fabricating these materials. Synthesis of Ag-NPs employing either micro-organisms or plant extracts has emerged as an alternative approach.

Silver nanoparticles are potential anticancer agents [29]. Cytotoxicity studies of silver nanoparticles using plant extracts: *Melia dubia* - human breast cancer cell line [30], *Malus domestica* (apple) extract - MCF7 [31], *Inonotus obliquus* (Chaga mushroom) extract - A549 human lung cancer (CCL185) and MCF7 human breast cancer (HTB22) cell lines [32], *Erythrina indica* - breast and lung cancer cell lines[33], *Piper longum* fruit - breast cancer cell lines [34], *Annona squamosa* and *Brassica oleracea*. var. botrytis - MCF-7 [35, 36] are reported. Silver nanoparticles synthesized using *Acalypha indica* Linn. shows only 40% cell inhibition against human breast cancer cells (MDA-MB-231) [37]. The MCF-7 cells lose their 50% viability with Ag-NPs (5 lg/mL) produced by *Dendrophthoe falcata* [38]. *Datura inoxia* Ag-NPs inhibits 50% proliferation of human breast cancer cell line MCF7 at 20 lg/mL after 24 h incubation by suppressing its growth, arresting the cell cycle phases, reducing DNA synthesis to induce apoptosis [39]. Nuclear condensation, cell shrinkage and fragmentation are noticed for MCF-7 cells treated with *Sesbania grandiflora* mediated Ag-NPs (20 lg/mL) after 48 h in Hoechst staining. *Morinda citrifolia* root extract-mediated Ag-NPs (100 lg) produced 100% death of HeLa cell lines [40]. Longer exposures to *Eucalyptus chapmaniana* Ag-NPs (0.02 mmol/mL) resulted in 85 % cell death after 24 h incubation [41, 42]. The viability of HL-60 cells decreased to 44% after 6 h treatment with *Rosmarinus officinalis* Ag-NPs at 2 mM and cell death increased to 80% after 24 h incubation [41, 42].

Cytotoxic activity was extremely sensitive to the size of the nanoparticles produced using *Iresine herbstii* leaf and the viability measurements decreased with increasing dosage (25 - 300 lg/mL) against the HeLa cell lines [43]. *Piper longum*-mediated silver nanoparticles exhibit a significant cytotoxic effect (94.02 %) at 500 lg/mL on HEp-2 cell lines [44]. The therapeutic effect of silver nanoparticles may elicit through manipulation of their size, shape, elemental composition, charge and surface modification or functionalisation, leading target particles to specific organs [45]. Owing to the significance of silver nanoparticles in cancer treatment and the necessity for newer breast cancer drugs, the present work spotlights the cytotoxic potential of the synthesized biogenic silver nanoparticles.

Amid the cropping methods of nano synthesis, biogenic synthesis finds healthier application in pharmacology due to the nontoxic nature of the source of capping material used. *Alternanthera sessilis* is a weed growing on a variety of soil types. Its young shoots and leaves are ingested as vegetables.

Phytochemical screening reveals the presence of reducing sugars, steroids, terpenoids, saponins, tannins and flavonoids in *A. sessilis* [46]. The herb possesses antioxidant [47], anti-inflammatory [46], antipyretic [48], haematinic [49], hepatoprotective [50], antiulcer [51], antimicrobial [52], diuretic [53] and cytotoxic [54] activities. The herb is also reported as febrifuge, galactagogue, abortifacient, and used in the treatment of indigestion [55]. The plant is reported to contain lupeol, a and b-spinasterol, b-sitosterol, stigmasterol, campesterol, handianol, 24-methylenecycloartanol, cycloeucalenol and 5a-stigmasta- 7-enol [56, 57].

Green synthesis of silver nanoparticles is evolving into an essential branch of nanotechnology as shown in **Fig. 2**. The Emerging significance of noble metal nanoparticles (gold and silver) in the area of nanotechnology due to their size features and advantages over available chemical imaging drug agents and drugs, inorganic particles have been examined as potential tools not only for medical imaging also for treating diseases [58]. Nanoparticles are structures ranging from approximately 1 - 100 nm [59, 60]. Nano size results in specific physiochemical characteristics such as high surface area to volume ratio, which potentially results in high reactivity [61].

Physical method, Chemical method and Biological method (green synthesis) are the three major methods for synthesis of nanoparticle. Chemical approaches are toxic and expensive. Thus, there is a growing need to develop environmentally and economically friendly processes, which do not use toxic chemicals in the synthesis protocols. Thus the role of green synthetic method was emerged which utilizes bacteria, fungi, algae and plants for the synthesis of silver nanoparticles [62]. The rate of reduction of metal ions using plants has been found to be much faster as compared to micro-organisms and resulting in the formation of stable metal nanoparticles due to environment friendly

approach. Green synthesis of silver nanoparticles has been reported using the extracts of plants such as *Jatropa curcas* [63], *Boswellia ovalifoliolata* [64], *Coriandrum sativum* [65], *Calotropis gigantean* [66], Bitter apple (*Citrullus colocynthis*) [67], *Cassia auriculata* [68], *Eucalyptus hybrida* [69], *Trianthema decandra* [70], *D. carota* extract [71] *etc*. Green synthesis of silver nanoparticles is an emerging field of research and it is already established that plant extract have high potential for production of silver nanoparticles with wide applications.

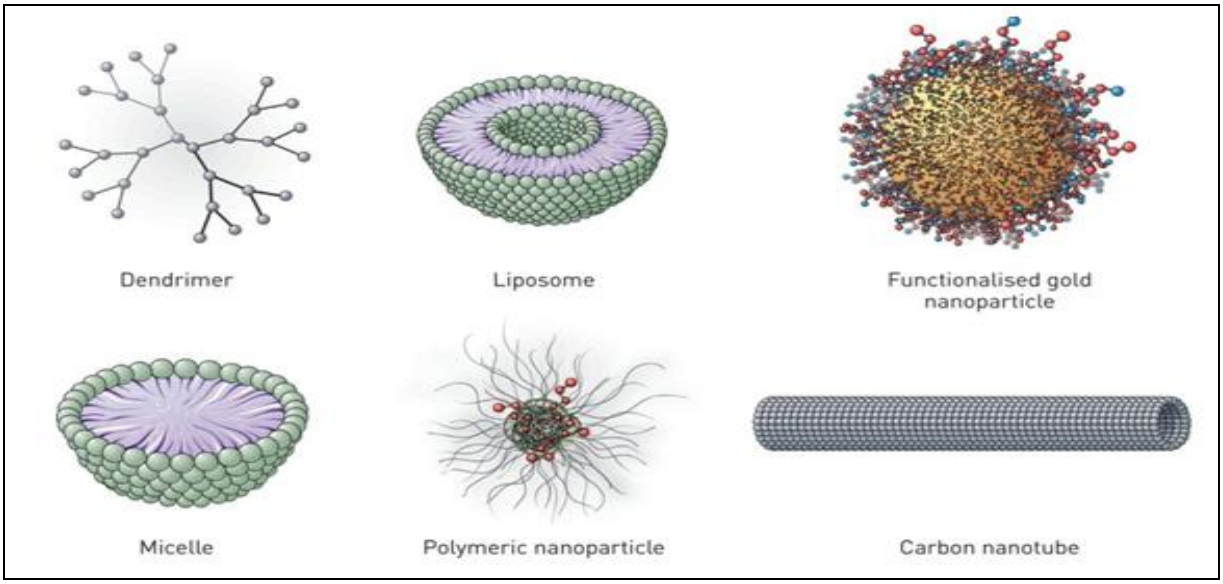

FIG. 2: BRANCHES OF SILVER NANOPARTICLES

1.1 Benefits of Green Synthesis Silver Nanoparticles: These biosynthetic methods have a numbers of benefits. They are simple, cost-effective, give high yields, and are environmentally friendly [22]. The concept of green chemistry was introduced to nanoparticles synthesis strategy to decline the use toxic chemicals and eliminate the production undesirable or toxic products. The well-known process for synthesis of metal nanoparticles is a chemical reduction of organic and inorganic solvents act as reducing agents *viz*. sodium borohydride, hydrazine, ascorbic acid, n-dimethylformaide and poly (ethylene glycol) (PEG) [72, 73] *etc*.

Green nanotechnology or green synthesis is nothing but an organic synthesis of nanoparticles using plant extracts and the synthesized nanoparticles are then known as biogenic nanoparticles. In numerous studies huge number of medicinal plants are used to synthesize the silver NPs [74, 75] like Mulberry leaves [76], *Alternanthera dentate* [77], *Ocimum sanctum*[78], *Azadirachta indica*[79], *Brassica rapa, Coccinia indica, Vitex negundo, Melia dubia* are used have already been used to synthesize and stabilize metallic nanoparticles, very particularly biogenic silver (Ag) nanoparticles.

2. Types of Green Synthesis Silver Nano-particles: There are different types of Ag-NPs, which categorized based on their applications:

1. Fluorescent nanoparticles can be used for multiplex simultaneous profiling of tumour biomarkers and for detection of multiple genes and matrix RNA with fluorescent *in-situ* hybridization. In breast cancer, three crucial biomarkers can be detected and accurately quantified in single tumour sections by use of nanoparticles conjugated to antibodies. In the near future, the use of.

2. Conjugated nanoparticles will allow at least ten cancer-related proteins to be detected on tiny tumour sections, providing a new method of analyzing the proteome of an individual tumour.

3. Supermagnetic nanoparticles have exciting possibilities as contrast agents for cancer detection *in-vivo*, and for monitoring the response to treatment.

4. Several chemotherapy agents are available as nanoparticle formulations, and have at least equivalent efficacy and fewer toxic effects compared with conventional formulations [14].

Although the number of different types of nanoparticlesis increasing rapidly, most can be classified into two major types on the basis of using materials to prepare Ag-NPs:

2.1. Organic Molecules as a Major Building Material Fig. 3: Liposomes, dendrimers, carbon nanotubes, emulsions, and other polymers are a large and well-established group of organic particles. Use of these organic nanoparticles has already produced exciting results [80, 81, 82, 83, 84, 85, 86].

Liposomes are being used as vehicles for drug delivery in different human tumours, including breast cancer [80, 81]. Dendrimers, used in MRI as contrast agents, have aided visualisation of various pathological processes [82, 83]. Conjugated with pharmacological agents and targeting molecules, organic nanovectors are potent vehicles for drug delivery and selective imaging of different human cancers [82, 83, 84, 85, 86].

Function of Organic/ Outer layer: This outside layer protects the core from degradation in a physiologically aggressive environment and can form electrostatic or covalent bonds, or both, spectroscopic signature, and a silica shell for protein conjugation **Fig. 3**. When illuminated with a laser beam, the reporter dye molecule produces a unique shift in the electromagnetic spectrum, which manifests as several sharp peaks and give the characteristic fingerprint of the reporter [87]. Colloidal gold nanoparticles with a size range of 55 - 60 nm can be optimized for surface enhancement at 632 - 647 nm excitation.

The benefit of using surface enhanced Raman scattering and nanoparticles in terms of selectivity and sensitivity has previously been shown by the detection of ultra-low concentrations (*i.e.*, 10^{-4} mol/m^3) of amfetamine sulfate in colloidal suspension [88].

2.2. Inorganic Elements, Usually Metals, as a Core Fig. 3: Most inorganic nanoparticles share the same basic structure - a central core that defines the fluorescence, optical, magnetic, and electronic properties of the particle, with a protective organic coating on the surface **Fig. 3**.

Function of Inorganic/ Core layer: Super-magnetic nanoparticles contain a metal core (*e.g*, iron, cobalt, or nickel) that is magnetically active, and are used as contrast enhancement agents to improve the sensitivity of MRI.

Magnetic particles, when coated with an organic outer layer, can also be conjugated to biomolecules and used as site-specific drug-delivery agents for cancer treatment. Iron-oxide based magnetic materials have been used widely in clinical practice as magnetic resonance agents and in studies of gene expression, angiogenesis imaging, and cellular trafficking [89, 90].

Metal nanoparticles in combination with fluorescent active molecules can be used for combined optical and magnetic imaging [91] with positively charged agents and biomolecules that have basic functional groups such as amines and thiols.

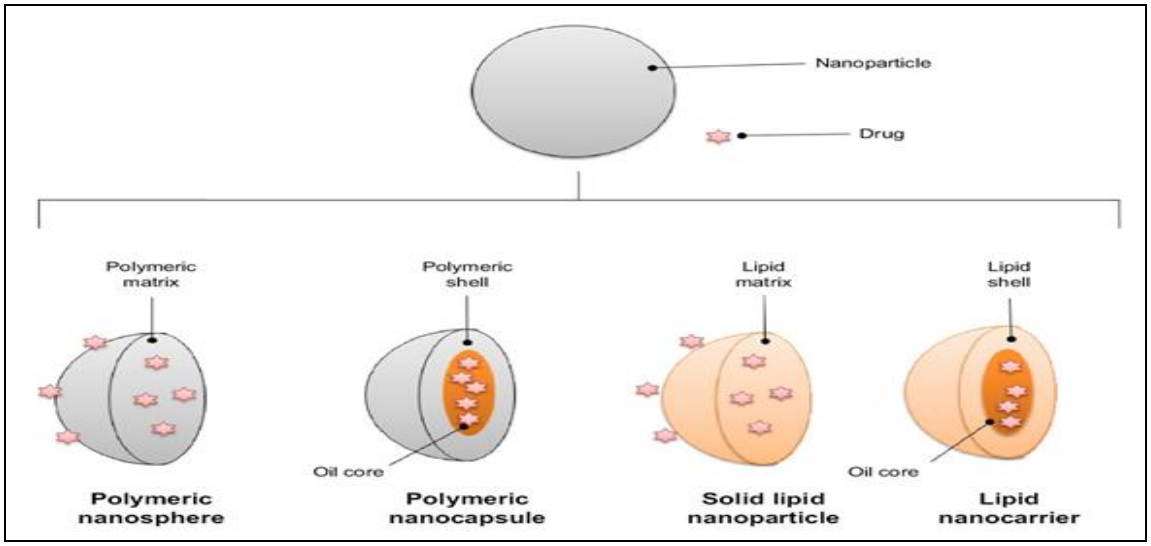

FIG. 3: TYPES OF GREEN SYNTHESIS SILVER NANOPARTICLE BASED ON CORE AND SHELL

2.3. Examples of Core with Coating Fig. 4: Several research groups have successfully linked fluorescent nanoparticles to peptides, proteins, and oligonucleotides [92, 93, 94, 95, 96]. Quantum dots are fluorescent nanoparticles with sizes of 2 - 10 nm that contain a core of hundreds to thousands of atoms of group II and VI elements (*e.g.*, cadmium, technetium, zinc, and selenide) or group III (*e.g.*, tantalum) and V elements (*e.g.*, indium) [97, 98].

Quantum dots containing a cadmium selenide core and a zinc sulphide shell, surrounded by a coating of a coordinating ligand and an amphiphilic polymer, are most commonly used for biological application **Fig. 4** [93, 98]. This structure enables quantum dots to emit powerful fluorescence that differs in nature from organic dyes. Quantum dots can be tuned to emit at between 450 nm and 850 nm (*i.e.*, from ultraviolet to near infrared) by changing the size or chemical composition of the nanoparticle. This so-called quantum confinement effect produces many quantum-dot colours, which can be visualised simultaneously with one light source. Quantum dots emit narrow symmetrical emission peaks with minimum overlap between spectra, allowing unique resolution of their spectra and measurement of fluorescent intensity from several multicolour fluorophores by real-time quantitative spectroscopy. These key advantages make it possible to label multiple molecular targets simultaneously by use of quantum dots both *in-vitro* and *in-vivo* [93, 98, 99, 100]. However, use of quantum dots in imaging and therapeutics *in-vivo* is limited by the toxic effects of the heavy-metal core [101].

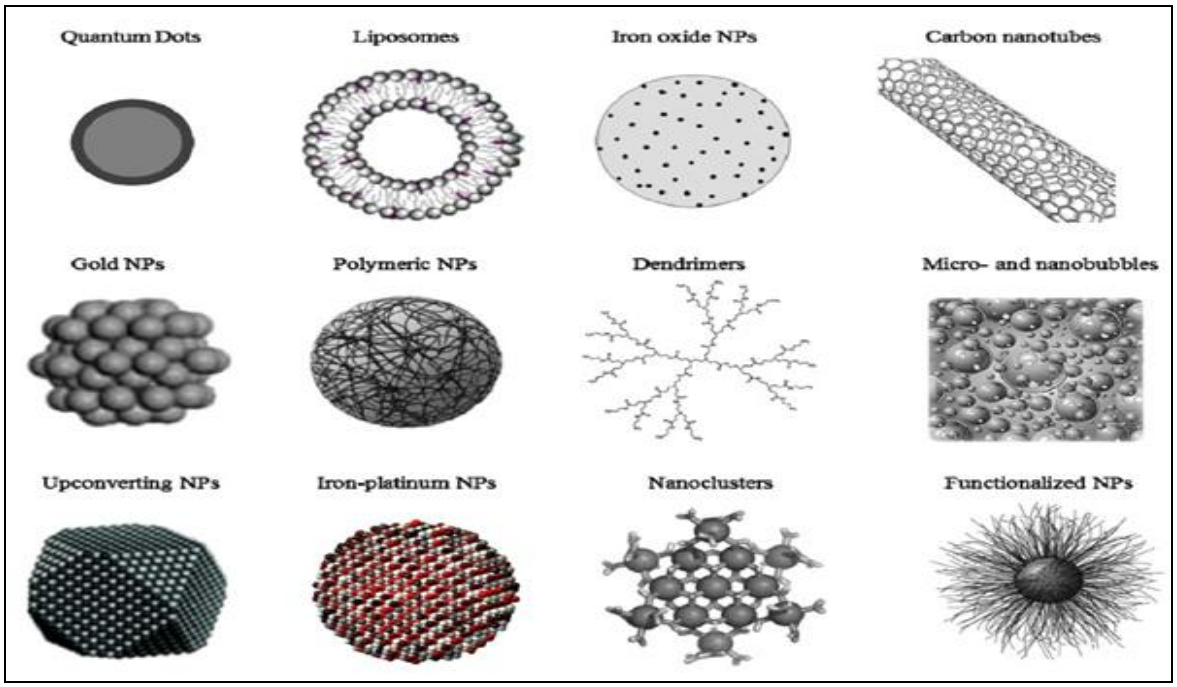

FIG. 4: EXAMPLES OF CORE WITH COATING

Surface-enhanced Raman scattering is another sensitive method for spectroscopic detection of multiple targets [102]. Modern surface-enhanced Raman scattering probes typically contain a metal core of silver or gold for optical enhancement, a reporter molecule for spectroscopic signature, and a silica shell for protein conjugation. When illuminated with a laser beam, the reporter dye molecule produces a unique shift in the electromagnetic spectrum, which manifests as several sharp peaks and give the characteristic fingerprint of the reporter [87].

Colloidal gold nanoparticles with a size range of 55 - 60 nm can be optimized for surface enhancement at 632- 647 nm excitation. The benefit of using surface enhanced Raman scattering and nano-particles in terms of selectivity and sensitivity has previously been shown by the detection of ultra-low concentrations (*i.e.*, 10^{-4} mol/m^3) of amphetamine sulfate in colloidal suspension [88]. Supermagnetic nanoparticles contain a metal core (*e.g.*, iron, cobalt, or nickel) that is magnetically active, and are used as contrast enhancement agents to improve the sensitivity of MRI.

Magnetic particles, when coated with an organic outer layer, can also be conjugated to biomolecules and used as site-specific drug-delivery agents for cancer treatment. Iron-oxide-based magnetic materials have been used widely in clinical practice as magnetic resonance agents and in studies of gene expression, angiogenesis imaging, and cellular trafficking [89, 90]. Metal nanoparticles in combination with fluorescent active molecules can be used for combined optical and magnetic imaging [91].

3. Advantages of Green Synthesis Silver Nanoparticle: A lot of literature has been reported to till date on biological syntheses of silver nanoparticles using microorganisms including bacteria, fungi and plants; because of their antioxidant or reducing properties typically responsible for the reduction of metal compounds in their respective nanoparticles.

3.1. The advantages of Green Synthesis over Chemical and Physical Methods are: [103]

- ✓ Environment friendly,
- ✓ Cost effective and
- ✓ Easily scaled up for large scale syntheses of nanoparticles, furthermore there is
- ✓ No need to use high temperature, pressure, energy and toxic chemicals.

Although; among the various biological methods of silver nanoparticle synthesis, microbe mediated synthesis is not of industrial feasibility due to the requirements of highly aseptic conditions and their maintenance.

3.2. The Advantages of use of Plant Extracts in Green Synthesis over Microorganisms are: [104]

- ✓ Ease of improvement
- ✓ Less biohazard and
- ✓ Elaborate process of maintaining cell cultures
- ✓ Reduce the cost of production and product.

It is the best platform for synthesis of nanoparticles; being free from toxic chemicals as well as providing natural capping agents for the stabilization of silver nanoparticles. Moreover, use of plant extracts also reduces the cost of micro-organisms isolation and their culture media which enhance the cost competitive feasibility over nanoparticles synthesis by microorganisms.

Hence, a review is compiled describing the bio-inspired syntheses of silver nanoparticles that provide advancement over physical and chemical methods which are eco-friendly, cost effective and more effective in a variety of applications especially in bactericidal activities.

4. Applications of Green Synthesis Silver Nanoparticles: Due to eco-friendly, cost-effective, high product yielding properties, Green synthesis of silver nanoparticles have been used most widely in the health industry, food storage, textile coatings and a number of environmental applications. Inspite of decades of its use, it is important to note that the evidences of toxicity of silver are still not clear. The specific application of green synthesis silver nanoparticles are describing below:

4.1. Baby Products: Currently silver is used in the expanding field of nanotechnology and appears in many consumer products that include baby pacifiers, acne creams, and computer's keyboard, clothing (*e.g.* socks and athletic wear) that protects from emitting body odor in addition to deodorizing sprays.

It is a well-known fact that silver nanoparticles and their composites show greater catalytic activities in the area of dye reduction and their removal. Kundu *et al*., studied the reduction of methylene blue by arsine in the presence of silver nanoparticle [105]. Mallick *et al*., studied the catalytic activity of these nanoparticles on the reduction of phenosafranine dye [106].

4.2. Antioxidant Effect: The toxicity of starch-coated silver nanoparticles was studied using normal human lung fibroblast cells (IMR-90) and human glioblastoma cells (U251). The toxicity was evaluated using changes in cell morphology, cell viability, metabolic activity, and oxidative stress. These nanoparticles produced ATP content of the cell causing damage to mitochondria and increased production of reactive oxygen species (ROS) in a dose-dependent manner.

DNA damage, as measured by single cell gel electrophoresis (SCGE) and cytokinesis blocked micronucleus assay (CBMN), was also dose-dependent and more prominent in the cancer cells [107]. The high frequency electrical behavior of nano-silver based conductors is up to 220 GHz [108].

4.3. Anti-viral Effect: Silver nanoparticles have proven to exert antiviral activity against HIV-1 at non-cyto-toxic concentrations, but the mechanism underlying their HIV-inhibitory activity has been not fully elucidated. These silver nanoparticles were evaluated to elucidate their mode of antiviral action against HIV-1 using a panel of different *in-vitro* assays [109]. Special interest has been directed at providing enhanced bio-molecular diagnostics, including SNP detection gene expression profiles and biomarker characterization. These strategies have been focused on the development of nano-scale devices and platforms that can be used for single molecule characterization of nucleic acid, DNA or RNA, and protein at an increased rate when compared to traditional techniques [110].

4.4. Anti-Microbial Effect: The Ag-NPs have been found to exhibit promising anti-microbial activity. Researchers have used several novel techniques to confirm and quantify the anti-microbial activity of Ag-NPs [111]. Silver is a well-known antimicrobial agent against a wide range of over 650 microorganisms from different classes such as gram-negative and gram-positive bacteria, fungi or viruses. More recently the metal is finding use in the form of silver nanoparticles. In ancient Indian medical system (called Ayurveda), silver has been described as therapeutic agent for many diseases. In 1884, during childbirth it became a common practice to administer drops of aqueous silver nitrate to newborn's eyes to prevent the transmission of Neisseria gonorrhea from infected mothers. Out of all the metals with antimicrobial properties, it was found that silver has the most effective antibacterial action and is least toxic to animal cells [112]. The antimicrobial properties of silver nanoparticles have also been exploited both in the medicine and at home. Silver sulfadiazine creams use sometimes to prevent infection at the burn site and at least one appliance company has incorporated silver into their washing machines [112].

In this study [106], the application of silver nanoparticles as an antimicrobial agent was also investigated by growing *E. coli* on agar plates and in liquid LB medium, both supplemented with silver nanoparticles [113]. Single silver nanoparticles were applied to investigate membrane transport in living microbial cells (*P. aeruginosa*) in real times [114]. The triangular silver nanoparticles fabricated by nanosphere lithography indeed function as sensitive and selective nanoscale affinity biosensors. Silver nanoparticles synthesized through green method have been reported to have biomedical applications as well as in controlling the pathogenic microbes. In a study, silver nanoparticles were synthesized using aqueous *Piper longum* fruit extract. The aqueous *P. longum* fruit extract and the green synthesized silver nanoparticles showed powerful antioxidant properties *in-vitro* antioxidant assays [115]. Silver metal has been used widely across the civilizations for different purposes. Many societies use silver as jewellery, ornamentation and fine cutlery. Silver as jewellery, wares and cutlery was considered to impart health benefits to the users. Silver has a long history of anti-microbial use to discourage contamination of microbes dating back to the Phoenicians who used silver as a natural biocide to coat milk bottles.

Silver became commonly used in medical treatments, such as those of wounded soldiers in World War I, to deter microbial growth [116]. The medical properties of silver have been known for over 2000 years [117]. Silver is generally used in the nitrate form to induce antimicrobial effect but when silver nanoparticles are used, there is a huge increase in the surface area available for the microbes to be exposed to. The antimicrobial properties of silver nanoparticles depend on first, size and environmental conditions (size, pH, ionic strength) and secondly on capping agent.

4.4.1. Mechanisms of Antimicrobial Effect of Green Synthesis Silver Nanoparticles: The exact mechanisms of antimicrobial or toxicity activities by silver nanoparticles are still in investigation and a well debated topic. The positive charge on the Ag ions is suggested vital for antimicrobial activities. In order for silver to have any antimicrobial properties, it must be in its ionized form. In its ionized form, silver is inert but on coming in contact with moisture it releases silver ions [118]. Ag^+ ions are able to form complexes with nucleic acids and preferentially interact with the nucleosides rather than with the phosphate groups of nucleic acids. Thus, all forms of silver or silver containing compounds with observed antimicrobial properties are in one way or another sources of silver ions (Ag^+); these silver ions may be incorporated into the substance and released slowly with time as with

silver sulfadiazine, or the silver ions can come from ionizing the surface of a solid piece of silver as with silver nanoparticles [119, 120]. There is some literature showing the electrostatic attraction between positively charged nanoparticles and negatively charged bacterial cells [121] and they are suggested to be most suitable bactericidal agent [122, 123].

These nanoparticles have been shown to accumulate inside the membrane and can subsequently penetrate into the cells causing damage to cell wall or cell membranes. It is thought that silver atoms bind to thiol groups (ASH) of enzymes forming stable SA Ag bonds with thiol containing compounds and then it causes the deactivation of enzymes in the cell membrane that involve in trans membrane energy generation and ion transport. It was proposed that Ag(I) ion enters the cell and intercalates between the purine and pyrimidine base pairs disrupting the hydrogen bonding between the two anti-parallel strands and denaturing the DNA molecule. Bacterial cell lysis could be one of reason for its antibacterial property. Nanoparticles modulated phosphotyrosine profile of bacterial peptide that in turn affects signal transduction and inhibited growth of micro-organisms. Antibacterial effect is dose-dependent and is independent of acquisition of resistance by bacteria against antibiotics. *E. coli* cells treated with silver nanoparticles found to be accumulated in the bacterial membrane which results in the increase in permeability and death of cell.

Gram-positive bacteria are less susceptible to Ag^+ than gram-negative bacteria. This is due to; the gram positive bacterial cell wall made up of peptidoglycan molecules and has more peptidoglycan than gram-negative bacteria. As cell wall of gram positive is thicker, as peptidoglycan is negatively charged and silver ions are positively charged; more silver may get stuck by peptidoglycan in gram-positive bacteria than in gram-negative bacteria. The decreased liability of gram positive bacteria can also simply be explained by the fact that the cell wall of gram-positive bacteria is thicker than that of gram-negative bacteria [116]. Other mechanisms involving interaction of silver molecules with biological macromolecules such as enzymes and DNA through an electron-release mechanism [124] or free radical production [116] have been proposed. The inhibition of cell wall synthesis as well as protein synthesis shown to be induced by silver nanoparticles has been suggested by some literatures with the proteomic data having evidence of accumulation of envelope protein precursor or destabilization of outer membrane, which finally leads to ATP leaking [125].

Nanosilver is a much effective and a fast-acting fungicide against a broad spectrum of common fungi including genera such as *Aspergillus*, *Candida* and Saccharomyces [126]. The multi-resistant pathogens due to antigenic shifts and/or drifts are ineffectively managed with current medications. This resistance to medication by pathogens has become a stern problem in public health; therefore, there is a strong requirement to develop new bactericides and virucides. Silver is having a long history of use as an antiseptic and disinfectant and is able to interact with disulphide bonds of the glycoprotein / protein contents of microorganisms such as viruses, bacteria and fungi. Both silver nanoparticles and silver ions can change the three dimensional structure of proteins by interfering with disulphide bonds and block the functional operations of the microorganism [127, 128, 129]. Advancement of this route (green synthesis) over chemical and physical method is that it is cost effective, environment friendly, easily scaled up for large scale synthesis and there is no need to use high energy, pressure, temperature and toxic chemicals [128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138]. The use of environmentally benign materials like bacteria, fungi, plant extracts and enzymes for the syntheses of silver nanoparticles offers numerous benefits of eco-friendly and compatibility for pharmaceutical and other biomedical applications as they do not use toxic chemicals for the synthesis protocol [112]. These disadvantages insisted the use of novel and well refined methods that opened doors to explore benign and green routes for synthesizing nanoparticles

4.5. Antibacterial Effect: There is worldwide interest in silver nanoparticles (Ag-NPs) synthesized by various chemical reactions for use in applications exploiting their antibacterial activity against gram positive bacteria, *Lactobacillus fermentum* [139], *Streptomyces sp.* [140], *Bacillus cereus* [141], *Brevibacterium case* [142], *S. aureus* [143], *B.*

licheniromis [144], and gram negative bacteria, *E. coli* [145], *Entrobacteria* [146] and *Ureibacillus thermo sphaerius* [111, 147], even though these processes exhibit a broad range of toxicity in vertebrates and invertebrates alike. To avoid the chemical toxicity, biosynthesis (green synthesis) of metal nanoparticles is proposed as a cost-effective and environmental friendly alternative.

Ag-NPs were prepared by an eco-friendly hydrothermal method using an *Aloe vera* plant extract solution as both a reducing and stabilizing agent. *Aloe vera* leaf extract is a medicinal agent with multiple properties including an antibacterial effect. Moreover the constituents of *Aloe vera* leaves include lignin, hemicellulose, and pectins which can be used in the reduction of silver ions to produce as *Aloe vera* Ag-NPs with antibacterial activity. Prepared *Aloe vera* Ag-NPs were characterized using XRD and SEM. Additionally, an agar well diffusion method was used to screen for antimicrobial activity. MIC and MBC were used to correlate it. SEM was used to investigate bacterial inactivation. Then the toxicity with human cells was investigated using an MTT assay. The synthesized *Aloe vera* Ag-NPs were crystalline with sizes of 70.70 ± 22 - 192.02 ± 53 nm as revealed using XRD and SEM. The sizes of Ag-NPs can be varied through alteration of times and temperatures used in their synthesis. These Ag-NPs were investigated for potential use as an antibacterial agent to inhibit pathogenic bacteria. Their antibacterial activity was tested on *S. epidermidis* and *P. aeruginosa*. The results showed that Ag-NPs had a high antibacterial which depended on their synthesis conditions, particularly when processed at 100 ºC for 6 h and 200 ºC for 12 h. The cytotoxicity of Ag-NPs was determined using human PBMCs revealing no obvious cytotoxicity. These results indicated that *Aloe vera* Ag-NPs can be effectively utilized in pharmaceutical, biotechnological and biomedical applications [148].

An eco-friendly approach for the preparation of silver nanoparticles (Ag-NPs) from silver nitrate solution using aqueous *Eriobotrya japonica* leaf extract was investigated. The reduction of silver ions in solution was monitored using UV-visible absorption spectroscopy, and the surface Plasmon resonance of Ag-NPs at 435 nm was observed. The proper condition to biosynthesize Ag-NPs using *E. japonica* leaf extract was optimized by UV-visible absorption spectroscopy and dynamic light scattering measurement (DLS). The biosynthesized nanoparticles were characterized using transmission electron microscopy (TEM), scanning electron microscopy (SEM), energy dispersive X-ray spectroscopy (EDX), DLS, X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR). XRD and EDX analyses confirmed the crystalline character of Ag-NPs and the presence of elemental silver. The prepared Ag-NPs were spherical in shape, and their average particle size determined by TEM was about 20 nm. Furthermore the Ag-NPs were found to exhibit effective antibacterial activities against *Escherichia coli* and *Staphylococcus aureus* [149].

4.6. Anti-Fungal Effect: The Ag-NPs exhibited antifungal action against various fungi [150, 151]. Actual mechanism behind the antifungal activity is not fully. The disrupting the structure of the cell membrane by destructing the membrane integrity, thereby the inhibition of the budding process has been attributed to be responsible for the antifungal action of Ag-NPs against *C. albanicans* species [152]. The shape of the Ag-NPs has a significant effect on the anti-microbial activity [153].

4.7. Anti-Parasitic Effect: The Ag-NPs have been found to be effective larvicidal agents against dengue vector *Aedes aegypt* [154], and *Culex quinquefasciatus* [155], filariasis vector *C. quinquefasciatus* [156] and malarial vector *A. subpictus* [157], *Aedes aegypti* [158], *A. subpictu* [156] and other parasites [159, 160]. No attempt has been made to propose a proper mechanism for anti-parasitic action of Ag-NPs. Denaturation of sulfur containing proteins and phosphorus containing DNA by Ag-NPs, leading to denaturation of organelles and enzymes is believed to be responsible for the larvicidal activity [161].

4.8. Anti-Fouling Effect: The Ag-NPs synthesized from *Rhizopus oryzae* fungal species have been used for treating contaminated water and adsorption of pesticides [162] and that from *Lactobacillus fermentum* cells have been used as anti-bio fouling agent [163]. The Ag-NPs are being used to treat many environmental concerns like; air disinfection, water disinfection, ground water and

biological water disinfection and surface disinfection [164].

4.9. Other Applications: There have been several reports on the use of Ag-NPs in the field of medicine. The Ag-NPs have been used as therapeutic agents [165], as glyconano sensors for disease diagnosis [166] and as nano carriers for drugs delivery [167]. Reports are also available on the use of Ag-NPs in radiation therapy [168], in H_2O_2 sensor [169], in ESR Dosimetry [170], as heavy metal ion sensors [171] and as catalyst for reduction of dyes such as methylene blue [172].

4.10. Anti-cancer Effect: Cancer is one of the most serious problems and health issue in the world. It has been observed that more than one out of three people will develop some form of cancer in their entire lifetime, thus resulting in economic and life quality constraints at the different levels of society. Based on the origin, there are variety of cancer exist, such as thyroid, prostate, bladder cancer, kidney cancer, pancreatic, breast cancer, melanoma, leukemia with all types, oral cancer, colon-rectal combined cancer, *etc*. In cancer cells are divided into other new cells and grow hysterically, forming invasive tumours and invading nearby healthy parts of the body [173]. In pursuit of an effective cancer treatment, chemotherapy represents an advantageous approach over radiotherapy and surgery; it ensures that anticancer drugs like vinblastine, doxorubicin, taxol, and cisplatin among others reach all the diseases sites including micrometastatic injuries.

The systematic administration of cytotoxic drugs during chemotherapy currently faces two major problems

- ✓ The dose-limiting toxicity against healthy tissues and
- ✓ The intrinsic or acquired multidrug resistance (MDR) by the patient. Moreover, it is known that anticancer drugs cause genotoxicity, thus producing DNA damage and prevent chromosomal replication.

These treatments are expensive and severe side effects like bone marrow problems, hair loss, nausea, emesis and fatigue [174]. To diminish or avoid these side effects, nanoparticles are used as anticancer therapeutics.

As there are numerous methods like, chemical precipitation sol-gel process, reverse micelles technique, hydrothermal method and biological methods used to synthesize silver nanoparticles but biological methods / green synthesis are eco-friendly, easy, cost effective and don't involve the use of any toxic and expensive chemicals. The various plants are used in synthesis of silver nanoparticles for anticancer activity against human cancer cell lining [175].

4.10.1. Cytotoxic Effect on Cervical Carcinoma Cells: Sreekanth *et al*., [176] synthesized the silver nanoparticles from *Saccharina japonica* extract act as reducing and capping agent and their cytotoxic effect on cervical carcinoma cells was examined. They use the confocal laser scanning microscopy and fluorescence microscopy to examine the apoptotic features such as reduction in nuclear volume and cytoplasm condensation. This study revealed that, 0.16 and 0.32 mg/ml silver nanoparticles could be toxic to healthy cells. In their work, *Saccharina japonica* extract mediated silver nanoparticles showed a clear cytotoxic effect on HeLa cells and clear concentration- response relationship was also observed. The fluorescence microscopy study was performed to determine the cytotoxic effect of Ag-NP's. Cytotoxicity was directly related to apoptosis induction.

Jeyaraj *et al*., [177] reported the green synthesis of Ag- NP's from *Podophyllum hexandrum* royal leaf extract with spherical shaped with average size of 14 nm. They determine the cytotoxic effects of green synthesized Ag-NP's on human cervical carcinoma cells by quantification of ROS, RT-PCR, MTT assay, and western blotting techniques. Their study suggested that because of DNA damage, green synthesized Ag-NP's can inhibit the cellular mechanism of HeLa.

In this study, apoptosis was noticed with the morphological changes in the cell shape and chromatin condensation. The ability of green synthesized silver nanoparticles to induce apoptosis was examined by using acridine orange and ethidium bromide staining. The stained cells in this study were examined to early apoptotic, nonviable cells, late apoptotic cells and viable cells. By comparing the positive control cisplatin the green synthesized silver nanoaprticles shows the greater

apoptotic effect. Furthermore, the effects green synthesized silver nanoparticles against HeLa cells gross nuclear morphology was observed under fluorescence microscopy after Hoechst 33258 staining. After the treatment with 20 mg/ml Ag-NP's for 24 h, HeLa cells shows the apoptotic characteristics like cell shrinkage, nuclear condensation, and fragmentation.

Rosarin *et al*., [178] studied the Anti-proliferative effect of amla extract mediated silver nanoparticles against Hep2 cell lining. They synthesize the spherical and cubic PE-Ag-NP's with an average size of 188 nm. This study indicates that, Ag-NPs are capped with biomoecules of Amla with enhanced cytotoxicity laryngeal cancer cells through oxidative stress and apoptotic function on Hep2 cancer cells.

4.10.2. Lung Cancer Treatment Effect: Silver nanoparticles (Ag-NPs) have now been recognized as promising therapeutic molecules and are extending their use in cancer diagnosis and therapy. This study demonstrates for the first time the antitumor activity of green-synthesized Ag-NPs against lung cancer *in-vitro* and *in-vivo*. Cytotoxicity effect was explored on human lung cancer H1299 cells *in-vitro* by MTT and trypan blue assays. Apoptosis was measured by morphological assessment, and nuclear factor-κB (NF-κB) transcriptional activity was determined by a luciferase reporter gene assay. The expressions of phosphorylated stat3, Bcl-2, survivin, and caspase-3 were examined by Western blot analysis.

Ag-NPs showed dose - dependent cytotoxicity and stimulation of apoptosis in H1299 cells. The effects on H1299 cells correlated well with the inhibition of NF-κB activity, a decrease in Bcl-2, and an increase in caspase-3 and survivin expression. Ag-NPs significantly suppressed the H1299 tumor growth in a xenograft severe combined immuno-deficient (SCID) mouse model. The results demonstrate the anticancer activities of Ag-NPs, suggesting that they may act as potential beneficial molecules in lung cancer chemoprevention and chemotherapy, especially for early - stage intervention [179].

4.10.3. Colon Cancer Treatment Effect: Recently, the biosynthesis of nanoparticles has been well explored which draws attention to its possible biomedical applications especially in cancer therapy. In the current study, the novelty in the biosynthesis of silver nanoparticles (Ag-NPs) using honey bee extract has been explained. This study was also aiming at investigating the anti-colon cancer activities of the biogenic Ag-NPs along with its capping biomolecules *in-vitro*. The obtained biogenic Ag-NPs were well characterized by X-ray diffraction (XRD), energy dispersive X-ray (EDX), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). It was found that the formed Ag-NPs have spherical shape with size range from 12 to 18 nm embedded in honey bee biomolecules.

The cytotoxicity results of Ag-NPs on peripheral blood mononuclear cells (PBMC) indicated that the obtained Ag-NPs could be used safely with concentrations upto 39 µg/ml. On the other hand, the potentialities of the biogenic Ag-NPs against colon cancer proliferation recorded 60% inhibition using its nontoxic dose with a down regulation of the expression of Bcl2 and survivin gene. By the extraction of Ag-NPs capping biomolecules to explain the exact fraction that is responsible for the anticancer properties, it was found that both Ag-NPs and its capping biomolecules have anti-proliferative effects with a priority to the naked Ag-NPs [180].

4.10.4. Breast Cancer Treatment Effect: Some breast cancers express protein biomarkers (*e.g.*, oestrogen receptor, progesterone receptor, and ERBB2) on which therapeutic decisions are made. Semiconductor fluorescent nanocrystals, such as quantum dots, have been conjugated to antibodies, allowing for simultaneous labelling and accurate quantification of these target proteins in one breast tumour section [181]. The use of nanoparticles - not only quantum dots of different sizes and emission spectra, but also gold-containing nanoparticles (*i.e.*, Raman probes) - will allow the simultaneous detection and quantification of several proteins on small tumour samples, which will ultimately allow the tailoring of specific anticancer treatment to an individual patient's specific tumour protein profile [182]. The ability to detect molecular targets simultaneously on individual tumour samples could allow correlation between gene products and proteins in real time [183].

In addition, the effects of an individual treatment on expression of the target protein can be monitored before and after treatment, and provide a rapid method to measure the efficacy of a targeted therapy. Nano-technological approaches (*e.g,* nano-cantilevers and nanoprobes) are being actively investigated in cancer imaging [184]. Nanoparticles coupled with cancer specific targeting ligands can be used to image tumours and detect peripheral metastases [185]. Supermagnetic nanoparticles that have a metal core and are bioconjugated with antibodies against ERBB2 have shown promising results for simultaneous imaging and targeting of breast cancers therapeutically *in-vivo* [186].

In this regard, nanotechnology is expected to provide new avenues to overcome the genotoxicity associated with chemotherapy treatments. Suitable nanomaterials have been synthetized in an effort to improve the cell specificity of drug delivery and to reduce the DNA damage during chemotherapy treatment. Nanoparticles (NPs), such as silver nanoparticles (Ag-NPs), have been extensively applied in medical products like bandages, wound dressings, and linings catheters, due to their beneficial properties such as antibacterial, antifungal, and antiviral agents.

Ag-NPs have gained increased attention because of their therapeutic properties and applications as anticancer agents. In this regard, and in the line with nano-toxicology, several studies have been devoted to the study of Ag-NPs cytotoxicity and genotoxicity on different types of mammalian cell culture lines that include among others, human glioblastoma (U251), pluripotent human testicular embryonic carcinoma cells (NT2), human hepato-carcinoma cell (HepG2), normal human lung fibroblast (IMR-90) cells, and primary normal human peripheral blood mononuclear cells. Moreover, Ag-NPs have been used to trigger antitumor effects in Dalton's lymphoma as cites tumor models and human hepatoma cells.

On the other hand, raising concerns about reports on cytotoxic and genotoxic effects caused by the exposure of mammalian cell lines to Ag-NPs have led to intense research on the toxicity profile of Ag-NPs. Adverse effects include oxidative cell damage, apoptosis induced by the generation of reactive oxygen species (ROS), mitochondrial dysfunction, DNA damage, chromosomal aberrations, cell cycle arrest in the G2/M phase, activation of catabolic enzymes, cytoskeleton deformations, and inhibition of cell proliferation. Also, it has been demonstrated that cyto and genotoxic effects on mammalian cell lines exposed to Ag-NPs are time- and dose dependent [187]. At this stage, it is important to mention that diverse formulations of Ag-NPs available in the market differ in NP shape, size distribution, synthesis procedure, content of metallic silver, surface functionalization, and interactions with the capping agents. All these features affect the cytotoxicity as well as the chemical surface properties of Ag-NPs, which play a major role in the interaction of NPs with biological systems.

Indeed, it has been reported that cytotoxic and genotoxic effects depend, among others, on the size of the Ag-NPs as well as on the nature of the capping material [188, 189, 190]. Taking into consideration the reported cytotoxic effects of different formulations of Ag-NPs, we decided to use the commercial preparation Argovit™ as a source of Ag-NPs. This product is currently approved in Russia and other countries for their use in veterinary and human applications (*i.e.* cosmetics, hemostatic sponges for surgeries, and nutritional supplement) [20]. Therefore, in order to further investigate the potential medical applications of Ag-NPs formulated as Argovit as antiproliferative agent in cancer treatment, not only cytotoxic but also genotoxic effects must be addressed. In this study, Argovit Ag-NPs were thoroughly characterized by Fourier transform infrared spectroscopy by attenuated total reflectance (ATR-FTIR) and ultraviolet-visible (UV-Vis) spectroscopy, dynamic light scattering (DLS) and high-resolution transmission electron microscopy (HRTEM). Also, we tested the cytotoxic and genotoxic effect of Argovit Ag-NPs on a set of different cancer cell lines [191]. Moreover, nanoparticles conjugated to cancer-specific ligands could be used in early identification of tumours, allowing early intervention with a chemopreventive agent. Several nanotechnological approaches have been used to improve delivery of chemotherapeutic agents to cancer cells with the goal of minimizing toxic effects on healthy tissues while maintaining antitumour efficacy [14].

4.10.4.1. Risk factors of Breast Cancer: There are different types of risk factors are describing below which can cause the sign and symptoms of breast cancer.

4.10.4.1.1. Smoking: Jones *et al*., [192] has been reported the plausible biological reasons exist regarding why smoking could affect breast cancer risk, but epidemiological evidence is inconsistent. In this study, 102, 927 women recruited 2003-2013, with an average of 7.7 years of follow-up, 1815 developed invasive breast cancer. The HR (reference group was never smokers) was 1.14 (95% CI 1.03 - 1.25; P = 0.010) for ever smokers, 1.24 (95% CI 1.08 - 1.43; P = 0.002) for starting smoking at ages < 17 years, and 1.23 (1.07–1.41; P = 0.004) for starting smoking 1 - 4 years after menarche. Breast cancer risk was not statistically associated with interval from initiation of smoking to first birth (P-trend = 0.97).

Women with a family history of breast cancer (ever smoker *vs* never smoker HR 1.35; 95% CI 1.12 - 1.62; P = 0.002) had a significantly larger HR in relation to ever smokers (P for interaction = 0.039) than women without (ever smoker *vs* never smoker HR 1.07; 95% CI 0.96 - 1.20; P = 0.22). The interaction was prominent for age at starting smoking (P = 0.003) and starting smoking relative to age at menarche (P = 0.0001). They have concluded that the smoking was associated with a modest but significantly increased risk of breast cancer, particularly among women who started smoking at adolescent or peri-menarcheal ages. The relative risk of breast cancer associated with smoking was greater for women with a family history of the disease.

4.10.4.1.2. Use of Prescription Drugs and Risk of RBC Transfluids: Thomsen *et al*., [193] has been reported the several frequently used prescription drugs may affect bleeding risk. In this study, they have investigated the use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), and statins and risk of postoperative red blood cell transfusion in breast cancer patients. Using Danish population-based registries, they identified a cohort of women who underwent surgery for primary breast cancer (n = 22,238) during 2005 - 2012 and ascertained their use of aspirin, NSAIDs, SSRIs, and statins.

For each drug, patients were categorized as users if they filled ≥1 prescription in the 60 days prior to surgery. They calculated the 14 - day risk of red blood cell transfusion and relative risks (RRs) with 95% confidence intervals (CIs), comparing users with nonusers for each drug and adjusting for age, cancer stage, and Charlson comorbidity index score. At the end of cohort study, the results described, 1385 (6.2%) women were aspirin users, 1794 (8.0%) were NSAID users, 1110 (4.9%) were SSRI users, and 2053 (9.1%) were statin users. The overall risk of red blood cell transfusion was 1.3%.

The 14 - day risk of RBC transfusion was 3.5% among aspirin users versus 1.1% among aspirin nonusers (adjusted RR = 1.9, 95% CI: 1.4-2.7), and 1.8% among SSRI users versus 1.2% among SSRI nonusers (adjusted RR = 1.2, 95% CI: 0.7-1.9). Red blood cell transfusion risk was increased among NSAID users, but not in a sensitivity analysis with a 30 - day exposure window. Red blood cell transfusion risk was not increased among SSRI and statin users. So, they have concluded that the primary breast cancer surgery confers a low risk of RBC transfusion. Still, use of aspirin and possibly NSAIDs, but not SSRIs and statins, is associated with increased red blood cell transfusion. This increased risk is not explained by differences in age, stage, or comorbidity level.

4.10.4.1.3. Bone Microenvironment: Amanatullah *et al*., [194] has been described that the approximately 70% of all breast cancers express the estrogen receptor, and are regulated by estrogen. While the ovaries are the primary source of estrogen in premenopausal women, most breast cancer is diagnosed following menopause, when systemic levels of this hormone decline. Estrogen production from androgen precursors is catalyzed by the aromatase enzyme.

Although aromatase expression and local estrogen production in breast adipose tissue have been implicated in the development of primary breast cancer, the source of estrogen involved in the regulation of estrogen receptor-positive (ER^+) metastatic breast cancer progression is less clear. In this study, Bone is the most common distant site of breast cancer metastasis, particularly for ER^+ breast cancers. We employed a co-culture model using trabecular bone tissues obtained from total hip

replacement (THR) surgery specimens to study ER^+ and estrogen receptor-negative (ER^-) breast cancer cells within the human bone micro-environment. Luciferase-expressing ER^+ (MCF-7, T-47D, ZR-75) and ER^- (SK-BR-3, MDA-MB-231, MCF-10A) breast cancer cells were cultured directly on bone tissue fragments or in bone tissue-conditioned media, and monitored over time with bioluminescence imaging (BLI). Bone tissue-conditioned media were generated in the presence vs. absence of aromatase inhibitors, and testosterone. Bone tissue fragments were analyzed for aromatase expression by immuno-histochemistry.

They have concluded with the results, ER^+ breast cancer cells were preferentially sustained in co-cultures with bone tissues and bone tissue-conditioned media relative to ER^- cells. Bone fragments analyzed by immunohistochemistry revealed expression of the aromatase enzyme. Bone tissue-conditioned media generated in the presence of testosterone had increased estrogen levels and heightened capacity to stimulate ER^+ breast cancer cell proliferation.

Pretreatment of cultured bone tissues with aromatase inhibitors, which inhibited estrogen production, reduced the capacity of conditioned media to stimulate ER^+ cell proliferation. These results suggest that a local estrogen signaling axis regulates ER^+ breast cancer cell viability and proliferation within the bone metastatic niche, and that aromatase inhibitors modulate this axis. Although endocrine therapies are highly effective in the treatment of ER^+ breast cancer, resistance to these treatments reduces their efficacy. Characterization of estrogen signaling networks within the bone microenvironment will identify new strategies for combating metastatic progression and endocrine resistance.

4.10.4.1.4. Fair Color or White Women: Parada Jr *et al*., [195] have been examined the racial differences in the expression of eight genes and their associations with risk of recurrence among 478 white and 495 black women who participated in the Carolina breast cancer study phase 3. In this study, breast tumor samples were analyzed for PAM50 subtype and for eight genes previously found to be differentially expressed by race and associated with breast cancer survival: ACOX2, MUC1, FAM177A1, GSTT2, PSPH, PSPHL, SQLE, and TYMS. The expression of these genes according to race was assessed using linear regression and each gene was evaluated in association with recurrence using Cox regression. In results, Compared to white women, black women had lower expression of MUC1, a suspected good prognosis gene, and higher expression of GSTT2, PSPHL, SQLE, and TYMS, suspected poor prognosis genes, after adjustment for age and PAM50 subtype. High expression (greater than median versus less than or equal to median) of FAM177A1 and PSPH was associated with a 63% increase (hazard ratio (HR) = 1.63, 95% confidence interval (CI) = 1. 09 - 2.46) and 76% increase (HR = 1.76, 95% CI = 1.15 - 2.68), respectively, in risk of recurrence after adjustment for age, race, PAM50 subtype, and ROR-PT score. Log2 - transformed SQLE expression was associated with a 20% increase (HR = 1.20, 95% CI = 1.03 - 1.41) in recurrence risk after adjustment.

A continuous multi-gene score comprised of eight genes was also associated with increased risk of recurrence among all women (HR = 1.11, 95% CI = 1.04 - 1.19) and among white (HR = 1.14, 95% CI = 1.03 - 1.27) and black (HR = 1.11, 95% CI = 1.02 - 1.20) women. At the end they have concluded that the racial differences in gene expression may contribute to the survival disparity observed between black and white women diagnosed with breast cancer.

4.10.4.1.5. Single - Nucleotide Polymorphisms (SNPs) Associations with Vitamin D: Huss *et al*., [196] has been suggested that vitamin D might protect from breast cancer, although studies on levels of vitamin D in association with breast cancer have been inconsistent. Genome - wide association studies (GWASs) have identified several single-nucleotide polymorphisms (SNPs) to be associated with vitamin D. The aim of this study was to investigate such vitamin D-SNP associations in relation to subsequent breast cancer risk. A first step included verification of these SNPs as determinants of vitamin D levels. In this study, the malmö diet and dancer study included 17,035 women in a prospective cohort.

Genotyping was performed and was successful in 4058 nonrelated women from this cohort in which 865 were diagnosed with breast cancer. Levels of vitamin D (25-hydroxyvitamin D) were available for 700 of the breast cancer cases and 643 of unaffected control subjects. SNPs previously associated with vitamin D in GWASs were identified.

Logistic regression analyses yielding ORs with 95% CIs were performed to investigate selected SNPs in relation to low levels of vitamin D (below median) as well as to the risk of breast cancer. The results expressed that the majority of SNPs previously associated with levels of vitamin D showed a statistically significant association with circulating vitamin D levels. Heterozygotes of one SNP (rs12239582) were found to have a statistically significant association with a low risk of breast cancer (OR 0.82, 95% CI 0.68 - 0.99), and minor homozygotes of the same SNP were found to have a tendency towards a low risk of being in the group with low vitamin D levels (OR 0.72, 95% CI 0.52 - 1.00). Results from stratified analyses showed diverse associations with breast cancer risk for a few of the tested SNPs, depending on whether vitamin D level was high or low. At the end, they have concluded that the SNPs associated with vitamin D may also be associated with the risk of breast cancer. Even if such a risk is small, the allele frequency of the SNP variants is high, and therefore the population attributable risk could be substantial. It is also possible that Vitamin D levels may interact with genomic traits with regard to breast cancer risk.

4.10.4.2. Treatments of Breast Cancer: The following treatments are available to treat breast cancer and still, there is something more approach is require towards the breast cancer treatments to overcome the lacunae.

1. Albumin coated silver nanoparticles (AS-NPs) were synthesized, and their anti-cancerous effects were evaluated against MDA-MB 231, a human breast cancer cell line. The synthesized AS-NPs were characterized by spectroscopic methods. The morphological changes of the cells were observed by inverted, florescent microscopy and also by DNA ladder pattern on gel electrophoresis; the results revealed that the cell death process occurred through the apoptosis mechanism. It was found that ASNPs with a size of 90 nm and negatively charged with a zeta-potential of about -20 mV could be specifically taken up by tumor cells. The LD_{50} of AS-NPs against MDA-MB 231 (5 μM), was found to be 30 times higher than that for white normal blood cells (152 μM). The characteristics of the synthesized ASNPs included; intact structure of coated albumin, higher cytotoxicity against cancer cells than over normal cells, and cell death based on apoptosis and reduction of gland tumor sizes in mice. This work indicates that ASNPs could be a good candidate for chemotherapeutic drug [197].

2. The synthesis of silver nanoparticles using the aqueous extract of *Alternanthera sessilis* as a reducing agent by sonication, espousing green chemistry principles was described in this article. Biologically synthesized nanoparticle- based drug delivery systems have significant potential in the field of biopharmaceutics due to its smaller size entailing high surface area and synergistic effects of embedded biomolecules.

In the present work the cytotoxic effect of biosynthesized silver nanoparticles studied by MTT assay against breast cancer cells (MCF-7 cell line) showed significant cytotoxic activity with IC_{50} value 3.04 lg/mL compared to that of standard cisplatin. The superior activity of the silver nanoparticles may be due to the spherical shape and smaller particle size 10 - 30 nm as confirmed from transmission electron microscope (TEM) analysis. The data obtained in the study revealed the potent therapeutic value of biogenic silver nanoparticles and the scope for further development of anticancer drugs [1].

3. The green synthesis Ag-NPs from algal extract of Spirulina *platensis* inhibited the proliferation and induced apoptosis in MCF-7 breast cancer cell line. Due to weak chemical interaction with components of algal extract, the Ag-NPs are released *in vitro* leading to cytotoxic effects against human breast cancer cell. The algal extract capped nanoparticles solution was cytotoxic to MCF-7 cells in a concentration manner. The results suggest that Ag-NPs stimulate apoptosis through G0/G1 cell cycle arrest. This was obviously due to DNA damage and elevated indices of oxidative stress in AgNPs treated cells. Therefore, biologically synthesized

silver nanoparticles can be used for the treatment of cancer cells and can be exploited further to deliver drugs [198].

4. Green synthesis of silver nano particle is an environmentally friendly approach and it is already established that plant extract have high potential for production of silver nanoparticles with wide applications. *Catharanthus roseus* is one of the anti-cancerous plants belonging to the family Apocynaceae due to the presence of vinca alkaloids. The plant has certain chemical constituents which is known to have anti-bacterial and anticancer activity which acts as both capping as well as reducing agent, therefore the green-synthesised silver nanoparticles (Ag-NPs) from *Catharanthus roseus* has additive *in-vitro* cytotoxicity effect against human breast cancer (MCF-7) cells. Due to their nano size which might be contribute potent effect for breast cancer therapy. The current study is designed to reveal the *in-vitro* cytotoxicity effect of green-synthesized silver nanoparticles (Ag-NPs) against human breast cancer (MCF-7) cells. Ag-NPs were synthesized by using *Catharanthus roseus* leaf extract as a potent reducing agent.

Characterization is done by UV-Visible Spectroscopy, XRD Analysis, TEM analysis, and FT-IR Analysis. Cytotoxicity study was done by MTT assay in MCF-7 cell-line. The face centered cubic crystal structure crystalline and spherical silver nanoparticles of 07-33 nm in size are synthesized. The toxicity potential of the green synthesized Ag-NPs on human breast cancer cells has been examined using MCF-7 cell line by the3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide MTT assay. Green-synthesized Ag-NPs induce cytotoxicity on MCF-7 cell lines was found to be higher with increased concentration of Ag-NPs. Complete mortality rate was observed in 250 µg/ml concentration of Ag-NPs. IC_{50} of Ag-NPs was found to be 113.068 µg/ml [187].

5. In recent years researchers were attracted towards marine sources due to the presence of active components in it. Seaweeds were widely used in pharmaceutical research for their known biological activities. The biological synthesis method of silver nanoparticles (Ag-NPs) using *Padina tetrastromatica* seaweed extract and their cytotoxicity against breast cancer MCF-7 cells was reported in this study. The synthesized Ag-NPs using seaweed extract were subjected to X-ray Diffraction, UV–visible spectroscopy, fourier transform infrared spectroscopy, field emission scanning electron microscopy, transmission electron microscope, energy dispersive X-ray, zeta potential to elucidate the structural, morphology, size as well as surface potential parameters. An absorption peak at 430 nm in UV-visible spectrum reveals the excitation and surface plasmon resonance of Ag-NPs. FE-SEM micrographs exhibits the biosynthesized Ag-NPs, which are pre-dominantly round shaped and the size ranges between 40 - 50 nm. The zeta potential value of –27.6 mV confirms the stable nature of biosynthesized silver nanoparticles.

Furthermore, the biological synthesized Ag-NPs exhibited a dose-dependent cytotoxicity against human breast cancer cell (MCF-7) and the inhibitory concentration (IC_{50}) was found for Ag-NPs against MCF-7 at 24 h incubation. Biological method of synthesizing silver nanoparticles shows an environmental friendly property which helps in effective electrifying usage in many fields [199].

6. Liposomal Anthracyclines: Anthracyclines are some of the most active agents in the treatment of breast cancer [200] and are widely used in all stages of disease. However, the use of anthracyclines is limited by cardiac toxic effects, which occurs with high cumulative doses of these agents. Trastuzumab, a monoclonal antibody that targets ERBB2, has improved treatment of this aggressive form of breast cancer; [201, 202] however, its use is limited by a risk of cardiac toxic effects, which occur almost exclusively in patients previously treated with anthracyclines [201].

Liposomal anthracycline formulations were developed to improve the therapeutic index of conventional anthracyclines, while maintaining their widespread anti tumour activity. Three liposomal anthracyclines, all of which are nano-particles measuring about 100 nm, are being assessed in human cancers: liposomal dauno-rubicin, approved in the USA for the treatment of Kaposi's sarcoma; liposomal doxorubicin, which, in combination with cyclophosphamide, is approved for the treatment of metastatic breast

cancer in Europe; and pegylated liposomal doxorubicin, approved for both Kaposi's sarcoma and refractory ovarian cancer in the USA.

Both liposomal doxorubicin and pegylated liposomal doxorubicin have been compared with conventional doxorubicin in first-line treatment of patients with metastatic breast cancer [203, 204]. 297 patients with metastatic breast cancer, who had received no previous chemotherapy, were randomly assigned to 60 mg/m^2 liposomal doxorubicin or 60 mg/m^2 conventional doxorubicin, both in combination with 600 mg/m^2 cyclophosphamide every 3 weeks, until disease progression or unacceptable toxic effects. Efficacy did not differ significantly between the two groups (response rate 43% *vs.* 43%, median time to progression 5.1 *vs.* 5.5 months, and median survival 19 *vs.* 16 months). However, significantly fewer patients allocated to liposomal doxorubicin developed cardiac toxic effects compared with treated with conventional doxorubicin (6% *vs.* 21%, respectively, p = 0.0001) [203]. Overall, patients assigned liposomal doxorubicin were 80% less likely to develop cardiac toxic effects than were those assigned conventional doxorubicin. Liposomal doxorubicin was also associated with less neutropenia than was conventional doxorubicin. Pegylated liposomal doxorubicin was compared with conventional doxorubicin in patients with previously untreated metastatic breast cancer. 509 patients were randomly assigned to single-agent pegylated liposomal doxorubicin (50 mg/m^2 every 4 weeks) or doxorubicin (60 mg/m^2 every 3 weeks).

Both agents had similar efficacy, with response rates of 33% and 38%, and progression-free survival of 6.9 and 7.8 months, respectively [204]. The risk of cardiac toxic effects was significantly higher in patients assigned doxorubicin than in those assigned pegylated liposomal doxorubicin (hazard ratio 3.16, p<0.001). Neutropenia and gastrointestinal toxic effects were reported more commonly with doxorubicin, whereas palmar-plant are rythrodysaesthesia was more common with pegylated liposomal doxorubicin. Liposomal doxorubicin has been investigated in combination with trastuzumab in a phase I/II trial in patients with metastatic breast cancer. A response rate of 59% was noted, even though patients could have received trastuzumab previously.

Cardiac toxic effects were reported in two patients, both of whom had previously received conventional doxorubicin [205]. Anthracyclines are highly effective in ERBB2-positive breast cancer, [201] so the combination of liposomal formulations and trastuzumab warrant further study.

7. NAB paclitaxel: The taxanes paclitaxel and docetaxel are some of the most important agents in the treatment of solid tumours, and are widely used in all stages of breast cancer. Both drugs are highly hydrophobic, and have tobe delivered in synthetic vehicles (polyethylated castoroil for paclitaxel and polysorbate-ethanol for docetaxel). The toxic effects associated with both taxanes are increasingly recognized to be cause by these synthetic vehicles, and not the agents themselves [206, 207]. Several new formulations of these agents have been developed in an attempt to decrease the toxic effects associated with the taxanes.

NAB paclitaxel - a nanoparticle with a core containing paclitaxel surrounded by albumin, the naturally occurring vehicle for hydrophobic molecules - has shown efficacy in breast cancer. Preclinical studies [208] showed that NAB paclitaxel resulted in improved tumour penetration compared with conventional paclitaxel. In addition, it resulted in a higher plasma clearance and larger volume of distribution than did paclitaxel, consistent with a lack of sequestration by castor-oil micelles.

After phase I trials, a phase II trial12 in 63 patients with metastatic breast cancer showed a response of 48% to NAB paclitaxel at a dose of 300 mg/m^2 every 3 weeks. In a phase III trial 10 comparing NAB paclitaxel with conventional castor-oil-based paclitaxel, 460 patients with taxane-naive metastatic breast cancer were randomly assigned to castor-oil-based paclitaxel or NAB paclitaxel on a 3-weekly schedule until evidence of disease progression. Overall response was significantly higher in patients allocated NAB compared with those allocated the conventional formulation, irrespective of line of therapy (overall response in all patients 33% [95% CI 27.09 - 39.29] *vs.* 19% [13.58 - 23.76], p = 0.001; in patients receiving first-line treatment, 42% [32.44 - 52.10] *vs.* 27% [17.76 - 36.19], p = 0.029, for NAB paclitaxel versus conventional paclitaxel, respectively).

Time to progression was significantly longer for those allocated NAB paclitaxel than for those allocated to conventional paclitaxel (23 weeks *vs.* 17 weeks; p = 0.006). [10] Although overall survival was not significantly different in the patients as a whole (p = 0.374), patients in the second line setting had a significantly higher survival with NAB paclitaxel at 56 weeks compared with conventional paclitaxel at 47 weeks (p = 0.024).

Most importantly, tolerability improved with NAB compared with conventional paclitaxel. Although patients allocated. NAB paclitaxel did not receive any drugs before the trial, no hypersensitivity reactions were noted. In addition, grade IV neutropenia was significantly lower and incidence of grade 3 neuropathy significantly higher in patients allocated to NAB paclitaxel compared with those allocated to the conventional formulation (p<0.001 for both comparisons) (p<0.001). However, the NAB paclitaxel has been assessed on a weekly schedule in patients with heavily pretreated metastatic breast cancer. Responses were noted in patients who had given paclitaxel or docetaxel, or both, previously, and preliminary data suggest that neuropathy is lessened with this weekly schedule. In summary, this nanoparticle formulation of paclitaxel offers advantages over castor-oil-based paclitaxel, with an overall decrease in toxic effects, an absence of need for pretreatment, and enhanced efficacy.

8. Targeted Delivery of Tamoxifen: About two-thirds of breast cancers express hormone receptors, of which about 50% benefit from endocrine therapy. Tamoxifen remains widely used in all stages of breast cancer, in both premenopausal and postmenopausal women. It undergoes substantial metabolism, and an inability to get active drug into breast tumours might hinder its effectiveness. In another study. They have developed a tamoxifen-loaded, polymeric nanoparticle to increase tumour penetration. By use of a human breast-cancer xenograft model, they showed a significant increase in the level of tumour accumulation of tamoxifen in mice given the loaded nanoparticles, compared with those given an intravenous formulation. The use of drug-loaded nanoparticles offers the promise of improved tumour penetration, with selective tumour targeting, and a subsequent decrease in toxic effects [14].

9. Gene Therapy: Major strategies in breast-cancer gene therapy include transfer of tumour-suppressor genes, enhancement of immunological response, transfer of suicide genes, and bone-marrow protection by use of drug-resistance genes [209]. Breast-cancer genome abnormalities for which amplification or mutation of multiple genes, including ERBB2, P53, MYC, and cyclin D1 [210]. However, human gene-therapy techniques have been hampered by the fact that oligonucleotide-containing substances undergo rapid enzymatic degradation in human plasma.

Therefore, research is ongoing to identify the best delivery vehicle for gene therapy. Nanoparticle-based DNA and RNA delivery systems offer several potential advantages for gene delivery to various human tumours, including breast cancer.

A DNA plasmid can be coupled with cationic and neutral lipids to form lipid–nucleic-acid nanoparticles [211]. DNA molecules are encapsulated into the nanoparticle and are thus protected from degradation. In addition, conjugation of a polyethylene glycol molecule to the surface of the nanoparticle with targeted antibody increases gene delivery into tumour cells. Hayes and colleagues [211] have used this method to allow gene delivery to human ERBB2-positive breast-cancer cells using an ERBB2-directed antibody conjugated to a nanoparticle.

Another study [212] has shown successful transfer of E1A complexed with cationic liposome to human breast and ovarian cancers. Preclinical studies [213] have shown that adenovirus type 5 E1A is associated with anti-tumour activities by transcriptional repression of ERBB2.

Patients with breast or ovarian cancer (ERBB2-positive or low ERBB2 expressing) were treated in a phase I trial with this cationic liposome-mediated E1A gene-transfer system, given by injection either into the thoracic or peritoneal cavity. E1A gene expression in tumour cells was detected by immuno histo-chemical analysis and reverse-transcriptase PCR, suggesting successful gene transfer. In addition, E1A expression was accompanied by ERBB2 down regulation, an increase in apoptosis, and a reduction in proliferation [212]. Prahba and Labhasetwar [214] showed anti-proliferative activity

of wild-type P53-loaded nanoparticles in a breast-cancer cell line. Nanoparticles containing plasmid DNA were formulated by a multiple emulsion-solvent evaporation technique using a biocompatible polymer, poly (D, L-lactide-co-glycolide). Cells transfected with wild type P53 DNA-loaded nanoparticles showed significantly greater anti-proliferative effect than did those with naked wild type P53 DNA, resulting in anti-proliferative activity, which could be therapeutically beneficial in breast-cancer treatment [213].

Transfection of tumour cells with small-interfering RNA (siRNA) is a rapidly growing gene-silencing technology with great potential for clinical application. Inhibition of breast-cancer oncogenes results in induction of apoptosis and an increase of chemotherapy sensitivity in breast-cancer cells [215-216]. Stability and cellular uptake of siRNA can be greatly improved by adsorption to polyalkylcyano acrylate nanoparticles [217]. Nanoparticle - siRNA complexes directed to Ras matrix RNA selectively inhibited the proliferation of breast-cancer cells and markedly inhibited Ha-ras-dependent tumour growth in nude mice after injection under the skin. In addition, injection of a non-covalent siRNA-polyethylenimine targeting ERBB2 complex into the peritoneal cavity resulted in significant ERBB2 receptor down regulation in an animal, with a resultant reduction in tumour growth [218]. Despite this early stage of development, nanoparticle-based delivery systems have already shown significant benefits for targeted gene delivery, and indicate great potential for clinical use in breast-cancer therapy [14].

10. Doxorubicin has been formulated with a liposome delivery system into nanoparticle size, which maintains the efficacy of the drug and decreases cardiac toxic effects. One of these delivery systems, pegylated liposomal doxorubicin, is approved for treatment of refractory ovarian cancer and Kaposi's sarcoma in the USA. Nanoparticle albumin-bound (NAB) paclitaxel also has greater efficacy than conventional castor-oil based paclitaxel with an improved safety profile, and is approved in the USA for treatment of metastatic breast cancer.

Future Prospective: The plant extract mediated synthesis of silver nanoparticles is an essential aspect of nanotechnology and the applications of nanoparticles in various sectors. Green synthesis of metal nanoparticles are not time consuming compared to other biological process. There is still a need for commercially viable, economic and environment friendly route to find capacity of natural reducing constituent to form silver nanoparticles which has not yet been studied. Many reports have been published about the syntheses of silver nanoparticles using plant extracts like those as already discussed but among there is a significant variation in chemical compositions of plant extract of same species when it collected from different parts of world and may lead to different results in different laboratories. This is the major drawback of synthesis of silver nanoparticles using plant extracts as reducing and stabilizing agents and there is need to resolve this problem. On identifying biomolecules present in the plant which are responsible for mediating the nanoparticles production for rapid single step protocol to overcome the above said problem can give a new facelift towards green synthesis of silver nanoparticles.

CONCLUSION: An increasing awareness towards green chemistry and use of green route for synthesis of silver nanoparticles lead a desire to develop environment-friendly techniques. Benefit of synthesis of silver energy efficient, cost effective; provide healthier work places and communities, protecting human health and environment leading to lesser waste and safer products.

Green synthesized silver nanoparticles have significant aspects of nanotechnology through unmatched applications. It has quantified benefits and economically advantageous over the chemical and physical methods as well as among the microbes also. For the synthesis of nanoparticles employing plants can be advantageous over other biological entities which can overcome the time consuming process of employing microbes and maintaining their culture which can lose their potential towards synthesis of nanoparticles. There is still a need for commercially viable, economic and environment friendly route to find capacity of natural reducing constituent to form silver nanoparticles which has not yet been studied.

There is a significant variation in chemical compositions of plant extract of same species when it collected from different parts of world and may lead to different results in different laboratories. Hence in this regard; use of plant extract for synthesis can form an immense impact in coming decades.

ACKNOWLEDGEMENT: The authors acknowledge the Amrutvahini College of Pharmacy, Sangamner, Maharashtra - 422608, India for providing financial assistance. The authors also want to thank the library of the college for providing e-resources available. I am very thankful to College for supporting me at each and every step of my work.

CONFLICT OF INTEREST: The authors declared that there is no conflict of interest.

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How to cite this article:
Chintamani RB, Salunkhe KS and Chavan M: Emerging use of green synthesis silver nanoparticle: an updated review. Int J Pharm Sci & Res 2018; 9(10): 4029-55. doi: 10.13040/IJPSR.0975-8232.9(10).4029-55.