Chapter

Optimization of Biogenic Synthesis of Colloidal Metal Nanoparticles

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Abstract

Nanotechnology which deals with the synthesis and characterization of dispersed or solid particles in nano-metric range has emerged out to be a novel approach due to its ample applications in biomedical fields. The advancements in the field of nanotechnology and substantial evidences in biomedical applications have led the researchers to explore safe, ecofriendly, rapid and sustainable approaches for the synthesis of colloidal metal nanoparticles. This chapter illustrates superiority of biogenic route of synthesis of nanoparticles over the different approaches such as chemical and physical methods. In biogenic route, plants and microorganisms like algae, fungi, yeast, actinomycetes etc. act as "bio-factories" which reduce the metal precursors and play a crucial role in the synthesis of nanoparticles with distinct morphologies. Thus, the need of hazardous chemicals is eliminated and a safer and greener approach of nanoparticles synthesis can be adopted. This chapter also outlines the effect of optimization of different parameters mainly pH, temperature, time and concentration of metal ions on the nanoparticle synthesis. It is evident that the optimization of various parameters can yield nanoparticles with desired properties suitable for respective biomedical applications.

Keywords: colloidal metal nanoparticles, biogenic synthesis, biomedical applications, optimization, nanobiotechnology

1. Introduction

Ever since the origin of human civilization as early as 500 BC, nanomaterials (NMs) have been used for a range of applications, biomedicinal formulations being a crucial one [1]. Due to small size ranging from 1 to 100 nm, high aspect ratio, distinguished magnetic, optical, electrical, mechanical properties as compared with bulk materials of their same kind, MNs are being widely explored for their possible range of biomedical applications. In addition, ease of synthesis, control over size and morphology have revolutionized the field of nanobiotechnology [2]. The convergence of nanotechnology and biotechnology has led to the emergence of innovative and powerful field that explores the possibility of utilizing various NMs for biomedical applications [2]. The manipulations of macro materials resulting

in unique properties of NMs have attracted biomedical researchers to utilize these properties in pharmaceutical fields such that the NMs would play a momentous role and indeed add to the functionality of original compound [3]. The NMs and nano-biomaterials are being extensively used in biomedical field for diagnostics, imaging, drug delivery and as prostheses and implants due to their superior biocompatibility to artificial polymeric materials [4]. The metallic and non-metallic nanoparticles (NPs) used extensively in biomedicines are derived from sources such as bulk metals, non-metals, chemicals, plants and microbes. Owing to well-defined and tunable size, shape, molecular weight and uniform dispersity of lipids and proteins based NMs, they are used for the fabrication of nanocarriers such as liposomes, micelles and dendrimers for drug and gene delivery [5–7]. Depending upon the type of NMs, the pharmaceutical ingredient can be either encapsulated or attached onto the surface of such nanocarriers in such a way that, irrespective of the water solubility, the pharmaceutical ingredient can be delivered to the target site and protected against degradation [2]. Presently, almost 175 exclusive nanomedicinal products for the treatment of cancer and infectious diseases are at different stages of clinical trials soon to be launched into the market [8]. Concurrently, surgical blades, suture needles, contrast-enhancing agents for magnetic resonance imaging, bone replacement materials, wound dressing materials, anti- microbial textiles, *in vitro* molecular diagnostic chips, microcantilevers, and microneedles are already out in the market [9].

The capsules PillCamESo and PillCam Colon, sized as that of a normal pill act as a substitute for the traditional endoscopy technique. These contain a flashlight and a camera which is swallowed by the patient and the images of the gastrointestinal system are captured and sent wirelessly for further diagnostic purposes [10]. Similarly, 'microbots' structurally similar to flagella equal to half the human hair diameter are fabricated using computer chip technology. These comprise a magnetic head and can be controlled via an external magnetic field which delivers medicine to destroy tumors [11, 12]. Microbots can also relieve diabetes patients from the pain to test their blood multiple times every day and the inconvenience of self-testing to ensure stable blood-glucose levels. These could be used to retrieve data from varied locations of the body at the same time allowing continuous blood sugar level monitoring [2, 13]. The field of nanobiotechnology has also assisted insulin delivery systems to detect fluctuations in blood glucose levels and spontaneously modulate the adequate insulin release thereby maintaining normoglycemiea [14, 15]. A major drawback of non-specific drug delivery associated with conventional delivery system for cancer therapies can be overcome by using various NMs using metal NPs. To this end, metal NPs can be surface functionalized by attaching specific targeting moiety and imaging agents to target the cancerous cells [16]. This approach enables and enhances the efficiency in terms of not only timely detection of the cancerous cells but also treatment of tumors via targeted and specific release of drugs to yield maximum effectiveness with lower cytotoxicity to healthy cells [2]. In addition, nanobiotechnology has also contributed a solution for the treatment of a significant worldwide problem of hard tissue repair and regeneration by means of artificial bone scaffolds which mimic natural bone composition and structure [17, 18]. The use of biomimetics nano-assembly technology and additive manufacturing techniques make the scaffolds, cells and growth factors mimic the natural bone [19, 20]. Such scaffolds can also be used to deliver growth factors by acting as an alternative to extracellular matrix and other bioactive factors including small molecules, cytokines, peptides, proteins and genes [21, 22] to achieve controlled release and enhanced osteoblast proliferation and differentiation for stimulation of bone regeneration [23, 24].

2. Colloidal metal nanoparticles as important nanomaterials for various applications

In general terms, colloidal systems are heterogeneous systems in which very fine particles of one matter are scattered through another substance. Former is referred as "Dispersed Phase" while later as "Dispersion Medium" and both can be present in either of solid, liquid or gas states. Dispersed phase is completely insoluble in dispersion medium [25]. Colloidal NPs, as also called nanocolloids or solid colloidal particles, resemble a normal colloidal system where NPs act as dispersed phase. Being dispersed in the solvent medium, NPs are embroiled in some lively motions such as Brownian motions [26, 27]. As a consequence of their dominant characteristics over bulk correspondents the colloidal NPs, play vital role in number of applications [28]. The unique properties such as tunable size, configuration, structural arrangement, formulation, crystallinity and dimensions can deeply rectify the features of colloidal NPs according to the applications [29]. Colloidal NPs can be employed in prospective applications in the wide range of sectors including electronics, coatings, catalysis, packaging, biomedicine, biotechnology etc. In addition, the uses of colloidal NPs in biomedical field are increasing incredibly as they are being administrated with elegant attributes for healthier reactions with the biological circumstances and cope with on-demand requirements of *in vivo* diagnosis and therapies [30]. To boot, the fine size of NPs not only allows them to pass through the tissues or cells but also accesses them easily to target organs engrossing the novel biomedical applications at cellular level [31].

Magnetic NPs specifically iron oxide NPs are principally studied and utilized for their peculiar physicochemical, biological and magnetic features [32], remarkably stability, least perilous, significant magnetic vulnerability, severe saturation magnetism and biocompatibility [33]. Similarly, other magnetic NPs such as alloy, also known as bimetallic NPs of iron-cobalt (Fe-Co), iron-platinum (Fe-Pt) have high magnetic properties, super paramagnetism, high curie temperature [34, 35]. The exceedingly reported and mostly scrutinized uses of magnetic and bimetallic NPs are for target specific drug delivery [36, 37], in magnetic resonance imaging [38, 39] and to treat hyperthermia magnetically [40, 41].

Metallic NPs are the matter of curiosity that has been mesmerizing experts due to their extraordinary optical, electronic properties accompanied by its massive potential in nanotechnology. Nobel metal NPs of gold, silver, platinum, palladium, etc. have been used since ancient times for medicinal intents. Chemical inertness, ability to resist corrosion and oxidation even in moist air wholly justifies their uptake for biomedical applications [42]. Negative charge on the surface of gold NPs presents easy functionalization with organic compounds that offers further interactions with antibodies, drugs moieties or ligands for *in vitro* or *in vivo* drug delivery [43]. Likewise, silver NPs embrace distinct characteristics of being chemical inactivity, catalytic activity, high thermal and electrical conductive [44, 45]. The astonishing antimicrobial activity of silver NPs leads its utility in textile industries, wound healing dressings and as disinfectants [46, 47]. The employability of other metal NPs in bioimaging [48], biosensors [49], photothermal therapies [50] are growing day-by-day.

Metal oxide NPs such as titanium dioxide (TiO_2) and zinc oxide (ZnO) NPs are markedly used in paints, coatings, food coloring, beauty products, sunscreens etc. Equating with other metal oxide NPs, ZnO confers minimal toxicity to living cells so that there is increase in biomedical applications namely in diabetes treatment, wound healing, anti-inflammation treatment, anti-aging products, antibacterial activities, etc. [23, 51–53].

3. Methods for colloidal nanoparticles synthesis

Remarkable morphological, structural, magnetic, electronic and physico-chemical characteristics of colloidal NPs render them extraordinary for their uses in various fields such as physical, electrochemical, optical, environmental, biomedical fields etc. These peculiar properties of colloidal NPs depend on their source and route of synthesis process. Unremitting research in the field of nanotechnology have invented a range of ways to fabricate NPs. On the whole, these fabrication methods are segregated into three major groups, notably physical methods, chemical methods, and bio-assisted (also called biological and biogenic) methods in which NPs' synthesis is performed either by top-down approach or bottom-up approach. The top-down approach induces gradual trimming of bulk counterparts which invariably leads to the mass production of NPs. On the contrary, bottom-up approach deals with the consolidation of atoms and molecules to yield NPs with series of dimensions [54].

3.1 Physical methods

Physical methods principally rely on top-down approach where high energy emissions, mechanical pressure, thermal or electrical powers are employed for melting, mitigation, abrasion of bulk materials to beget NPs. These techniques are devoid of solvent contamination, produce monodispersed and reproducible NPs making suitable for few specialized applications. However, generation of waste byproducts along synthesis is one of the flaws of physical methods [55]. Some of the most commonly used physical methods to generate NPs are high energy ball milling, laser ablation, electrospraying, inert gas condensation, physical vapor, deposition, flame spray pyrolysis etc. These methods are pictorially depicted in **Figure 1**.

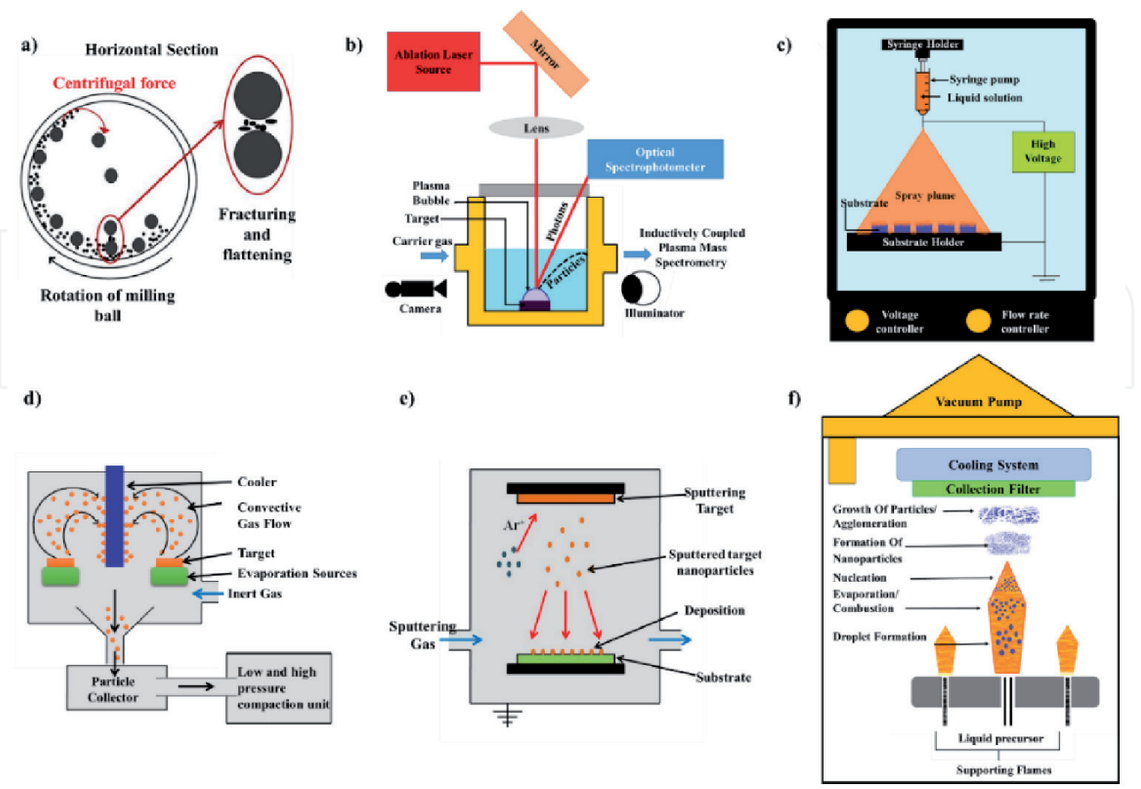

Figure 1.
Schematic representation of physical methods for synthesis of nanoparticles, (a) high energy ball milling, (b) laser ablation, (c) Electrospraying, (d) inert gas condensation, (e) physical vapor deposition, (f) flame spray pyrolysis.

High energy ball milling is a high pressure and thermal, sturdy and energy effective synthesizing manner in which immensely movable balls pass on their kinetic energy to the bulk materials. The crushing process disrupts the chemical bonds of the materials and rifts it into tiny particles to raise NPs with diverse conformation and dimensionalities [56]. High contamination prominently due to wear and tear crushing by balls, polydispersity in terms of irregular dimensions of synthesized NPs, aggregation and long milling time [57] are few of the disadvantages associated with high energy ball milling method.

Laser ablation is another physical method that either employs continuous laser or pulsed laser to strike on the material opted to break down into NPs. It is a flexible mode which involves series of melting, evaporation and ionization of material onto collector surface. The continuous bombardment of laser beam results into ablation of targeted material to micro and nanostructure materials [58]. Even though, NPs with high purity can be obtained through this method, its high cost, long operational time for production high input of power for extirpation of matter, difficulty in large scale production make this method not so popular [59].

The electrospraying mechanism is analogous to the electrospinning technique used to form fibers. In electrospraying, a blend of desired polymer solution and the solvent are filled in the syringe, subjected to high voltage electric field to split the solution into small charged nano-sized particles that are received by counter electrode. This technique provides flexibility over the size of NPs by varying the reaction conditions such as concentration of solution, electric field, conductivity, flow rate of liquid etc. [60]. Excess addition of cross linkages and low yield of NPs are some of the shortcomings of electrospraying technique [61].

Inert gas condensation is a very fundamental process that requires ultrahigh vacuum (UHV) conditions, inert gases like Helium (He) or Xenon (Xe) and a substrate cooled with liquid nitrogen. The target materials are first evaporated, then transferred along with inert gases and finally condensed on cooled substrate [62]. The agglomeration of condensed NPs, high cost associated with UHV conditions, difficulties related to maintaining clean vacuum situations, reproducibility and durability of working parameters etc. are some of the downsides of the techniques [63].

Physical vapor deposition is an ecologically compatible route that incorporates three successive vital steps such as pyrolysis of solid materials to convert into vapors, transmission of vaporized materials followed by nucleation and growth process. This integrated group of processes have been widely designed and used to fabricate NPs in addition to deposit thin films of nanometers to micrometers [64]. Despite the fact that the technique delivers marked advantages, the instability of precursor gas at ambient temperature as well as reaction temperature and high cost resulting from greatly controlled vacuum in chamber limits its use [65].

Flame spray pyrolysis is the recent and single step combustion process substantially operates to formulate compound and functional NPs. In this process, low volatile precursors are injected into highly sustainable flame with extreme temperature gradient where liquid precursor undergoes spray-to-particle or gas-to-particle pathway to form monodispersed NPs [55, 66]. The requirement of high stability and dispersibility of metal precursors and solvents, low volatility, relevant melting temperature limits the choice of materials and use of this technique [66].

3.2 Chemical methods

Chemical methods are certainly more favorable to synthesize colloidal NPs owing to their unaltered approach towards external stimuli. High yield and

reproducibility make them highly recommended. There are number of chemical methods, most of them are based on bottom up approach [67]. The chemical methods of colloidal NPs synthesis are diagrammatically represented in **Figure 2**. Sol–gel, plasma enhanced, chemical vapor deposition, polyol synthesis and hydrothermal synthesis are some of the primarily used chemical methods for synthesizing monodispersed NPs.

Colloidal solution of solid particles in liquid i.e. sol and liquid containing polymer i.e. gel are the two constituents of sol–gel method. The basic steps of the process are explicitly hydrolysis whereby the chemical bonds of precursors are deteriorated by water to form gel continued by condensation for genesis of sols in the liquid. In the end, the leftover liquid is drained to finalize the morphology of NMs [55, 68]. Owing to few flaws such as low abrasion resistance, poor bonding, exalted permeability and difficult control over porosity of technique, it becomes difficult to realize its industrial scale up [69].

In plasma enhanced chemical vapor deposition, also titled as plasma assisted chemical vapor deposition, plasma triggers the chemical reactions for formation of thin films and formulation of NPs as well. It is a well-known process conducted at lower temperature. The system is assembled by vacuum process unit, power supply, heater and precursor. The wide range of NPs can be formed via this method, for instance gallium nitride and so forth [70]. The expensive instrumentation, instability in damp conditions, presence of poisonous gases in plasma stream and lengthy process are some of the shortfalls of the method [71].

Polyol synthesis method fabricates colloidal NPs by using poly ethylene glycol as a medium to conduct the reaction. It also performs as solvent, reducing agent and integrating agent simultaneously with addition of protecting or capping agents externally [72]. The process is used to synthesize range of NPs of metals (platinum, palladium, silver, cobalt, etc.), metal oxide NPs (Zinc oxide, Cobalt oxide etc.) and magnetic, hybrid NPs as well [55]. However, the confined propensity of polyol to reduce precursors and slender stabilization of nonpolar metal surfaces by polar polyol are two major inadequacies with which the process has to dealt with and which diminishes the efficacy of the process [73].

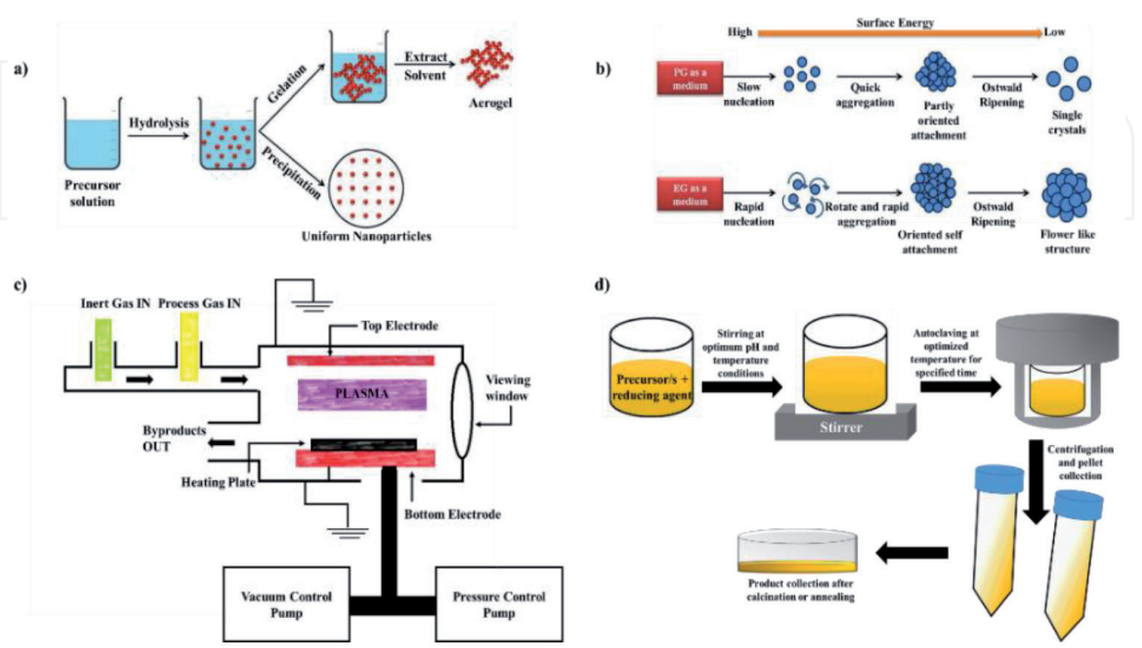

Figure 2.
Schematic representation of chemical methods for synthesis of nanoparticles, (a) sol–gel method, (b) polyol synthesis, (c) plasma enhanced chemical vapor deposition, (d) hydrothermal synthesis.

Hydrothermal synthesis method explores various temperatures and pressure environments to change the behavior of water in the vicinity. During synthesis, NPs are synthesized from colloidal system that comprises of two or more states of compound from solid, liquid or gas and added together with controlled conditions of pressure and temperature. This method is carried out either by batch hydrothermal process or continuous hydrothermal process to create NPs of metal oxide, lithium iron phosphate etc. The batch hydrothermal executes reaction optimal ratios of phases while other allows faster mode of reaction. One of the incredible advantages of the method is its capability to produce large quantities of NPs at a time with preferable properties [74, 75]. The reaction requires water in supercritical state, higher pressure and temperature which in turn limits the onsite examinations to get clarify with NPs synthesis [74].

3.3 Biological methods

Despite the fact that chemical and physical methods of colloidal NPs synthesis are awfully proficient, these methods anyway own copious shortcomings just like use of acutely life-threatening chemicals, non-polar organic solvents, diversified synthetic capping, reducing agents, etc. therefore, hamper their engagement in biomedical purpose. On top of this, synthesis via physicochemical routes fetches contamination on the exterior of NPs post synthesis that has brought up solemn disquietude regarding the unfavorable upshots of the chemically synthesized NPs on the environment and living cells [76, 77]. These limitations has forced researchers to look for novel, environment friendly alternatives to synthesize colloidal NPs [78, 79]. Green synthesis or biosynthesis is the most feasible substitute that makes the use of microorganisms and parts of plants instead of toxic and pernicious chemicals. Bacteria, fungi, algae and yeast are frequently used as bio-reactors that can hire a batch of anionic functional groups proteins, enzymes, reducing sugars, etc. to reduce metals salts to corresponding colloidal NPs [80, 81]. The different methods of biological synthesis of colloidal NPs are diagrammatically represented in **Figure 3**.

3.3.1 Advantage of nanoparticles synthesized via biological route

The routinely used NPs synthesis routes such as chemical and physical methods are not only energy and capital exhaustive but also employ the toxic chemicals and non-polar solvents for synthesis and synthetic additives or capping agents during the later process. These methods therefore rule out the application of such products in clinical and biomedical fields thereby creating a need for a safe, reliable, biocompatible and benign method for the production of NPs [82]. Worthy of the exceptional environment friendly nature, it has been reported that the NPs synthesis rate via biogenic methods are comparable to that of chemical methods [83–85].

For biomedical applications, it's obligatory that NPs must have depleted metal cytotoxicity and enhanced biocompatibility. Unlike physico-chemically synthesized NPs, green synthesized NPs are free from deleterious byproduct contamination that most often remain bound to the NPs surface and restraint their role in biomedical applications [86]. The decisive leverages that supports the biological routes for colloidal NPs synthesis are wide availability of key biological components, biocompatible reducing agents, capable of large scale synthesis with moderate temperature and pressure, dual working of enzymes or phytochemicals as reducing as well as stabilizing agents [87]. There are multiple superiorities concerned with bio-associated methods, uniquely expeditious and eco-friendly fabrication practices, less expensive and bio-tolerant nature of NPs. It does not demand for separate capping

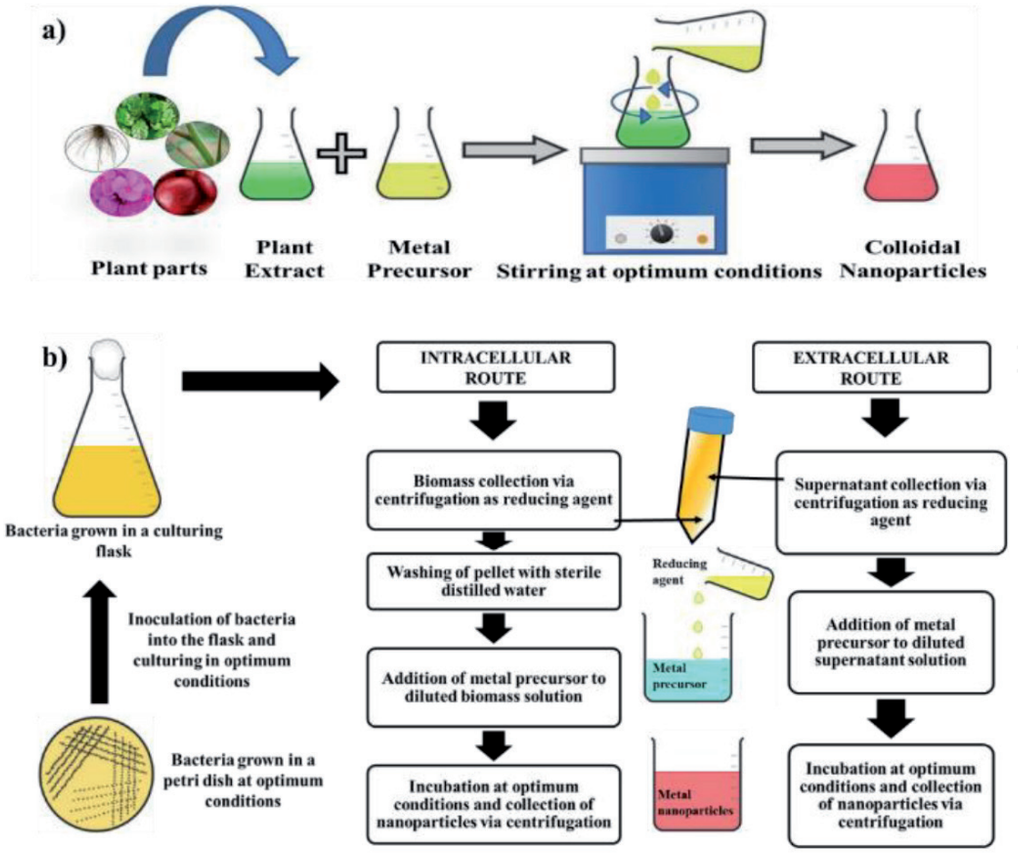

Figure 3.
Schematic representation of biological methods for synthesis of nanoparticles, (a) plant based synthesis, (b) microbial synthesis.

agents considering the potential of the plant's and the microorganism's components to act so [5]. On top of that, when NPs came in proximity of biological fluids while synthesis, they gradually and electively imbibe biomolecules establishing corona on the superficies that bestow additional potency and make them more efficient over uncovered NPs [88]. Precisely, medicinal plants are supposed to furnish the NPs with strengthened adequacy by entitling them with ample metabolites having pharmacological values [5, 89, 90]. As biosynthesized NPs are highly equipped with functional groups over the course of reaction, it eliminates additional steps required for physicochemical processes which automatically shorten the time period [91]. All of these supremacies make biosynthesis or green synthesis worth applicable.

3.3.2 General mechanisms of biological synthesis

3.3.2.1 Algal synthesis

Algae, either unicellular or multicellular, are autotrophic and aquatic photosynthetic organisms belonging to kingdom Protista. Depending upon their sizes that range from micrometer to macrometer, they are distinguished as microalgae or macroalgae and serve as extreme source of vitamins, minerals, and proteins. They have successfully drawn the utter attention by virtue of their competency to diminish the toxicity of metals accompanied by presence of bioactive components to stabilize the NPs; nonetheless the reports for algal synthesis of NPs are merely few, exclusively on iron oxide and zinc oxide [92]. Regardless the ongoing research on synthesis of NPs through different biological sources at greater extent, the detailed mechanism for the synthesis by algae is not revealed yet wholly. Studies so

far disclose that cell walls of seaweed are comprised of polysaccharides that carry hydrophilic surface groups like carboxyl, hydroxyl and sulfate groups [93]. Further, it holds abundant biomolecules, intrinsically proteins and enzymes which play the role of biocatalyst to convert metal ions into NPs, meanwhile, the other larger amphiphilic biomolecules act as capping agents to stabilize the NPs [94–97]. Some of the reported examples of algal synthesized NPs include AuNPs synthesized by brown seaweeds *Fucus vesiculosus* [98], and *Turbinaria ornate* [99]. A report by Khanehzaei et al. [100] explains the algal synthesis of copper and copper oxide NPs by extract of red seaweed *Kappaphycus alvarezii*.

3.3.2.2 Fungal synthesis

Fungal synthesis is the quite pertinent among remaining bio-synthesis methods, even than bacteria, in the wake of their phenomenal properties adeptness of NPs' synthesis with various dimensions [101]. Fungi viz. yeasts or molds are eukaryotic organisms that bear mycelia which allocate them extended surface area for metal ions acquaintance. Fortuitously, cell surface of fungi possesses chain of biomolecules and reducing agents which offers them numerous additional privileges [102]. Moreover, the NPs' configuration due to fungi is rapid considering the fact that fungi biomass proliferate rapidly than bacteria, and contrary to bacteria, fungi have superior endurance and metal bioaccumulation. In supplement, it provokes monodispersed synthesis of NPs with quite defined structures. Typically, fungal manufacture of metal NPs is judiciously cheaper, eco-friendly, engage uncomplicated down-streaming operation and no need of external stabilizing agent as fungal biomass itself function as capping agent as well [103, 104]. Bhainsa and D′ Souza in 2006 reported the synthesis of AgNPs by the fungus *Aspergillus fumigates* [105]. Metal oxide NPs have also been synthesized through the fungus synthesis for example, silicon dioxide (SiO_2), TiO_2 and ferric oxide (Fe_2O_3) NPs by fungus *Fusarium Oxysporum* [106].

Amidst other microorganisms that fall into kingdom fungi, yeast is the most examined species given the fact that extracellular synthesis is simpler to regulate and to manipulate in laboratory scenario [104]. As an example, Bharde and his coworkers have reported the reduction of TiO2 to NPs by means of fugal extract of *Saccharomyces cerevisiae* [106].

3.3.2.3 Bacterial synthesis

There are copious number of bacteria that smoothly sustain with harsh environmental conditions. Moreover, they can multiply and grow at extreme speed, their maintenance is cost effective and are easy to manipulate for synthesis. For this sake, they are being employed for the biogenic synthesis of colloidal NPs. Furthermore, the bacterial growth parameters especially temperature, oxygen supply and incubation time can be monitored with ease as they might affect the sizes of NPs [107].

The synthesis of NPs from bacteria is either intracellular or extracellular, depending on the site of synthesis. The intracellular synthesis deals with carrying of metal ions inside the microbial cell while in case of extracellular synthesis, metal ions are entrapped by the surface of cell to reduce it into corresponding NPs in presence of enzymes and other biomolecules [81]. The mechanism for formation of NPs differs with respect to the bacteria. When metal ions that are almost poisonous to bacteria, come in proximity, bacteria secrete specific proteins, enzymes and other biochemicals as a safeguard provision. To rectify the detrimental effect, bacteria modify metal ions into NPs by assorting not only dissolution of metal ions but also their redox behavior and extracellular sorption. Bacteria with S-layer and

Magnetotactic bacteria are best suited to harvest metal NPs whose cell wall surfaces are shielded with protein rich components [108, 109].

For *in vitro* synthesis of NPs using bacteria, initially convenient bacterial species is cultured for 1-2 days in shaking incubator or orbital shaker at optimal parameters incorporating temperature, pH, media concentration, shaking speed etc. The culture is then centrifuged to separate biomass. For intracellular synthesis biomass is collected, washed thoroughly with deionized water and dissolved in sterile water which in turn acts as a bacterial extract to reduce metal ions. Conversely, supernatant after centrifugation can also be used for extracellular synthesis of NPs [110].

3.3.2.4 Plant-based synthesis

As phytomining practices, plants with ability to hyper accumulate metals are planted on metal contaminated soils for uptake of metal ions. The metal ions disseminate into plant and travel to the convinced plant parts where primary and secondary metabolites such as terpenoids, flavonoids, phenolic acids, proteins, polysaccharides, organic acids etc. remold ions into metal NPs [5, 111, 112]. This approach is merely time consuming, tedious and retrieval of synthesized NPs is strenuous [111, 113]. The biogenic synthesis of NPs using plant extract or biomass is one of the most effective, rapid, absolute non-hazardous and ecofriendly methods. Nanoparticlesof noble metals, metal oxides, bimetallic alloys, etc. have been mainly synthesized *in vitro* by harnessing this method which is well reviewed by Iravani in 2011 [114].

For phytomediated biogenic synthesis, plant extracts are prepared from different parts of plants largely leaves, flowers, fruits, stem, roots, peels etc. [111, 113] and used as a source of reducing and capping agents. To accomplish this, the metal ion solution is subsequently added to extract where co-precipitation of metal ions with accessible functional groups is favored. The reaction parameters such as reaction time, temperature, pH, ration and concentration of metal salt influence the synthesis [115], therefore can be fine tunes. For example, ZnO NPs cane be formulated through leaf extract of *Corymbia citriodora* [116], peel extract of *Nephelium lappaceum* [117], root extract of *Polygala tenuifolia* [118].

4. Selection of biological agents for the synthesis of nanoparticles

Two main criteria for the selection of suitable plants for synthesis are selection of plant part on the basis of enzyme activities and biochemical pathways (for example: plants with heavy metal accumulations and detoxification properties); and setting the optimal conditions for enhanced cell growth and high enzyme activity [114].

According to Das and Brar [119], the plants are majorly preferred due to their exceptional reduction ability, yet, only the ethanobotanical conclusions are not the only basis for the selection of plants for the synthesis of NPs. These authors pointed out the fact that, the bio-reduction of the metallic cations can be a part of the plant's defensive reaction towards ionic stress. The chemical evolution of phytochemicals must thus be reconsidered to probe the possibility of exploiting different plant groups for biogenic synthesis. It was therefore suggested that, some representatives for each plant group must be picked and the protocol be standardized keeping in mind the process parameters and laboratory scale to commercial scale scaling up. It is important that the plant encompassing the desired properties must not fail at large scale level [119]. Some of the NPs synthesized from plants have the extreme potential in biomedical fields and should be considered for

scaling up purposes [120–122]. Das and Brar [119], also mentioned that instead of focusing on the advantages and disadvantages of biogenic synthesis routes such as efficiency, dual functionality, propensity, broad application etc.; it is important to have a broader perspective about the following parameters:

1. Clinical relevance must be checked by studying the previous well documented scientific reports.

2. Phylogenetic studies to set a reference plant.

3. In vitro study including cellular damage studies.

4. Precision in identifying the part of plant and mechanism

5. Geographical distribution studies to select a plant that does not have a very narrow distribution.

6. Genetic aspects, which is still an unexplored area.

7. This selection criteria is very feasible and applicable to all the plant groups and can bridge the gap exploitation of nature's ability and possibility to make biogenic synthesis more scalable.

Some bacterial species such as *Pseudomonas stutzeri* and *P. aeruginosa* have the ability to recourse specific defense mechanisms in order to deal with stress conditions like toxicity of heavy metal ions to survive and grow at high metal ion concentrations [123, 124]. Algae are economical contenders for the bioremediation and bioconversion of precious toxic metals into non-toxic nano forms due to their ability to accumulate and reduce metal ions into NPs [125]. Algae are preferred as they are convenient to handle, pose lower toxic effects to the environment and synthesize NPs at lower temperatures with great efficiency. Different algae widely used for the synthesis of NPs are: *Lyngbya majuscule, Spirulina platensis, Rhizoclonium hieroglyphicum, Phaeophyceae, Cyanophyceae, Rhodophyceae,* and *Chlorella vulgaris* [126, 127]. Fungi act as ideal biocatalysts for NPs synthesis and are preferred over bacteria due to greater potential of biologically active substances production [128]. Furthermore, fungal biomass are suitable for use in bioreactors as they can resist flow pressure, agitation and harsh conditions in chambers such as bioreactors and can exude extracellular reductive proteins suitable for employment in further steps of synthesis [102]. *Fusarium oxysporum* is one such fungi used for manufacturing NPs at industrial scale [129].

5. Preparation of extract and biomass for the synthesis of nanoparticles

The potential of phytosynthesis, a "green" synthesis approach is not yet completely utilized in full throttle for the colloidal NPs synthesis. As plants harbor a wide range of metabolites, it is possible to utilize plant tissue culture methods and optimizing the downstream processing techniques for the industrial production of NPs [130]. The part of the plant is chosen on the basis of desired application and the widely used plant parts of the part for extract preparation are leaf, seed, stem, fruit, root and flower. Initially, the test plant samples are collected, washed, dried and weighed. These are then chopped down into smaller pieces and soaked into sterile distilled water. This mixture is eventually incubated at optimized conditions

such as temperature, stirring speed etc. After a defined time span, the mixture is centrifuged at high speed, filtered using muslin cloth or syringe filters and stored in chilled conditions until future use. The filtrate is then diluted according to optimized conditions and used as a source of reducing and capping agents for the synthesis of NPs [131]. The plant extract thus prepared is mixed with defined ratio of metal salts at optimum conditions for defined time period resulting in NPs [132]. Not only the reaction conditions, but also the nature of extract and its concentration has a significant effect on the NPs synthesis and its quality [133].

Microbial route of synthesis of NPs has garnered enormous interest of researchers in the field of nanobiotechnology. Microorganisms including bacteria, fungi, actinomycetes, yeasts, and viruses are considered as bio-factories, owing to their inherent potential to produce NPs via. Extracellular or intracellular route of synthesis [102]. In case of extracellular synthesis, the microorganisms after subsequent growth of 1-2 days in shaking condition and optimum growth conditions are centrifuged to remove the biomass. The filter-sterilized metal salt solution is then added to the supernatant and incubated. The mixture is then centrifuged to collect the NPs pellet. For intracellular synthesis, the biomass is collected by centrifuging the micro-organisms culture grown in optimum conditions. The biomass pellet is washed and mixed with filter-sterilized solution of metal salt. Color changes in the reaction mixture are observed as a preliminary confirmation of NPs synthesis and further confirmed by spectrophotometric observations and highly sophisticated techniques. Further, similar to that of extracellular synthesis, the mixture is centrifuged to collect the NPs pellet [134].

In case of algae-mediated synthesis of metal NPs, the algal extract is prepared in sterile distilled water or an appropriate organic solvent by boiling it for specified duration. Further, the algal extract and the metal precursors are stirred at optimum conditions. Finally depending upon the mode of synthesis of NPs via algae, i.e. extracellular or an intracellular, the supernatant and biomass are used for the further process [135]. The bioactive agents such as polysaccharides, polyphones, proteins, and/or other reducing factors reduce the metal ions in case of extracellular synthesis of NPs [96, 98, 135, 136] while in case of intracellular synthesis, the algal metabolism via photosynthesis and respiration causes reduction of metal ions [135, 137, 138]. Eventually, the chromatic changes determine the synthesis of NPs as preliminary confirmation. In mycosynthesis i.e. fungi based synthesis, the metal precursors are used to treat fungus mycelium resulting in production of fungi metabolites and enzymes. These bioactive substances reduce toxic metal ions into non-toxic metal NPs [129]. The fungi are usually cultured on an agar plate and further transferred into a liquid medium. Depending upon the route of synthesis, either the biomass or the supernatant is mixed along with metal precursor to yield NPs [139, 140].

6. Effect of different parameters on synthesis of metal nanoparticles

6.1 pH

The pH is one of the most important biogenic synthesis reaction parameters that influence the particle size and morphology of NPs [141, 142]. The NPs can be tailored to the desired size by altering the pH of the reaction mixture which causes changes in the charge over secondary metabolites which has significant effect on their ability to adsorb the metal ions [86]. In case of microbial synthesis of NPs, the culture conditions play a significant role. The small-sized and monodispersed metal oxide NPs are formed in alkaline conditions rather than acidic conditions. This is

because more functional groups are available at higher pH that increase the binding ability and stability during nucleation and growth stages favoring the formation of less aggregated NPs [112]. Singh and Srivastava [143] observed a gradual blue shift (towards lower wavelength) in absorption maxima as the pH was increased from 3 to 7 indicating decrease in sizes of the NPs. Also, a red shift (towards higher wavelength) was observed when the pH was increased further from 7 to 11 The further increase in the pH was found to increase the NPs size. The reaction pH also has significant effect on particle morphology in terms of shape of the synthesized NPs [144]. Gericke and Pinches et al. [145] synthesized gold NPs from fungal cultures and observed that at pH 3, uniform sized spherical NPs of 10 nm were synthesized. When the pH was increased to 5, fewer smaller spherical particles were obtained, the morphology of most of the NPs changed to larger well defined triangular, hexagonal, spherical and rod like structures were also obtained. At higher reaction mixture pH 7 and 9, similar undefined structures were observed. Abeywardena et al. [146] employed sucrose solution based extraction of calcium to precipitate calcium carbonate nanostructures to study the effect of pH to yield nanostructures with different morphologies and sizes. The precipitation reaction was carried out at pH values of 7.5, 10.5 and 12.5 using CO_2 bubbling for carbonation as it promoted formation of smaller particles. Different morphologies such as catkin-like structure, spherical particles and rod-like formations; and tiny particles aggregated into large spheres were observed at pH 12.5, 10.5 and 7.5 respectively. Thus concluding that the alkaline pH is suitable for the formation of stable and less agglomerated nanoparticles. Aguilar et al. [147] studied the effect of different pH to yield stable silver nanoparticles using sugar cane bagasse extract. It was observed that acidic conditions (pH 3.5) were not favorable for the production of nanoparticles as the reaction yields mixture of submicron-sized silver (Ag) and silver chloride (AgCl) particles. At neutral pH, though the size of resultant nanoparticles dropped down in the range 8-30 nm, the mixture of Ag and AgCl particles still existed. In alkaline conditions i.e. pH 12, pure silver nanoparticles were obtained exhibiting excellent bactericidal and bacteriostatic properties against Gram positive and Gram negative bacteria. After the thorough inspection of the X-ray diffraction patterns and X-ray energy dispersive spectra (EDS) of the biosynthesized silver nanoparticles, it was evident that the Cl and S in the bagasse induces formation of side products such as AgCl and Ag@AgCl nanoparticles. While, at alkaline pH, the formation of such side products is avoided due to the interaction of Na ions of NaOH with Cl ions cane bagasse.

6.2 Temperature

Temperature is an equally important reaction parameters that significantly influence the biogenic synthesis of NPs [86]. For instance, the rate of synthesis increases at an elevated temperature as compared to that at room temperature eventually leading to higher product yield and crystalline NPs [148]. At elevated temperatures, the rate of reduction of metal ions increases and homogeneous nucleation of metal nuclei occurs facilitating the synthesis of NPs [149, 150]. Noteworthy, the required temperatures in physical methods of synthesis are greater than 350°C, while chemical reaction take place at temperatures as high as 350°C. On contrary, biogenic synthesis occur at considerably low temperatures in the range of 37°C-100°C [151]. In case of NPs synthesis using microorganisms, it is recommended that the microorganisms must be grown at the maximum possible temperature for optimal growth as the enzyme responsible for NPs synthesis shows enhanced catalytic activity at high temperatures and thus is more active [152]. Jameel et al. [153] highlighted the fact that reaction temperature affects the size,

morphology, and synthesis rate of platinum NPs. Also, higher number of nucleation centers are produced at elevated temperatures which enhances the biosynthesis rates. Temperature controls the rate of formation of NPs i.e. at higher reaction temperature yields faster rate of particle growth. As majority of NPs were synthesized within an hour, lower reaction temperatures were reported suitable to tune the size of NPs [145]. Harshiny et al. [154] studied the effect of temperature over the range 40 to 70°C, on the antioxidant activity of iron nanoparticles using *Amaranthus dubius* leaf extract. Initially, the antioxidant activity (AA%) increases with increase in temperature up to 50°C due to higher DPPH radical scavenging activities while antioxidant activity decreases beyond 50°C due to the degradation of the active constituent amino acids.

6.3 Time

Longer incubation time yield larger NPs with well-defined shapes, while smaller incubation periods cause smaller sized NPs [145]. Moreover, time has two distinct effects on the quality and potential of NPs synthesized via biogenic route. For instance, if the reaction mixture is incubated for longer time than the optimum, the NPs tend to aggregate causing increased particle size. Moreover, some NPs may even shrink upon longer storage [155, 156]. Sangaonkar et al. [157] studied the effect of incubation time by incubating the reaction mixture at different time periods ranging from 2 to 120 h using UV spectroscopy studies to conclude that 24 h was the optimum time for the synthesis of silver NPs using fruit extract of *Garcinia indica*. Similarly, the reaction set up by Krishnaprabha et al. [158] required two hours for the complete reduction of Au precursors into AuNPs using *Garcinia indica* fruit rind extract as a reducing agent. Thus, the parameter 'incubation time' is codependent on other reaction factors such as concentration of precursor and the biological agent used for preparation of extract. Manzoor et al. [159] studied the effect of nucleation time to reveal that increase in nucleation time results in increase in particle size and wider particle size distribution. It is also evident that intermediate stirring offers tunable particle size and narrow size distribution. Though the synthesis time varies with the precursor and extract used, a keen observation of the color of reaction mixture and analysis of SPR peaks can reveal the optimum time for the reaction. Increase in reaction time and color intensity of the reaction mixture along with prominent SPR peaks can reveal that large amount of metal ions get converted into (M+) zerovalent metal NPs (M^0) [160].

6.4 Concentration of metal ions

Concentration of metal ions is one of the key factors influencing the size of synthesized NPs. Usually, the reactions mixtures require just the right quantity of reactants, if the concentrations are slightly increased, the reduction mechanisms are hindered and accumulation of NPs would result in noticeable large aggregates of NPs [149]. Tuning the concentration metal ions in the reaction can be performed either by changing the volume of solvent or the amount of precursor. While, changing the concentration by varying the volume via dilution method is a straightforward method, changing the precursor quantity is subjected to maintaining the ratio between surfactant and precursor [161]. Moreover, researchers have reported that increase in precursor concentration may lead to either increase [162–165] or decrease [166, 167] in particle size. Recently, it has been experimentally proven that nanoparticle growth can be controlled as growth rate is dependent upon the surface reactions occurring at NPs, while at low concentrations, as the diffusion constant increases and the mass transferred is reduced, the growth rate is also reduced [161].

Lakkappa et al. [168], demonstrated the effect of silver precursor concentration on the formation of silver NPs using *Capparis Moonii* as a reducing agent. Their study concluded that higher concentration of the solution resulted in smaller sized NPs yet in wide range of size distribution. At higher metal ion concentrations, bathochromic shift causing change in intensity leads to broad SPR band, lower size dispersion and high aggregation; while, at lower concentrations yield high intensity, better absorbance and narrow SPR bands [160]. Thus, lower concentrations are preferred for the synthesis of metal NPs [169]. Sibiya and Moloto [170] carried out an experiment wherein two precursor salts were equipped for the formation of NPs. They found out that when the ratio of precursors was increased from 1:1 to 1:10, two distinct nanoparticle shapes: spherical and rod-like respectively were obtained. This change in morphology was attributed to the fact that, at higher precursor concentrations, the time required for NPs growth is longer, which therefore subsequently leads to different morphologies.

6.5 Other factors

The phytoconstituents (phenol, polyphenols, polysaccharides, tannins and anthocyanins), their quantity and volume of extract, influence the reduction of metal ions, average particle size, processing, synthesis time and stability of NPs. As the plant extracts act as reducing agent, their volume up to a certain extent works efficiently for the formation of stable metal NPs [149]. In plant based synthesis, as the composition of metabolites varies vastly in different plant parts of same species, the size of synthesized NPs varies with respect to part of plant used for extract preparation [171]. Singh and Srivastava [143] reported that as the concentration of black cardamom extract as a reducing agent was decreased, the size of resultant NPs increased.

In case of microbial route of synthesis, the enzymes and proteins existing in either the cell walls or cytoplasm reduce the precursor ions thereby aggregating atoms leading to formation of NPs [172]. Thus, such activity specific enzymes and proteins can be identified and isolated to facilitate reactions to be carried out in a cell-free environment producing NPs with tunable size and shape. Such experiments often yield triangular and hexagonal thin plate-like structures irrespective of source, being plant part or microorganisms [145, 173]. The pressure applied to the reaction mixture is also known to influence the shape and size of the resultant NPs [174]. Ambient pressure conditions accelerate the rate of reduction of metal ions using biological agents [175]. Plants are rich in various secondary metabolites which act as reducing and stabilizing agents and thus affect the NPs synthesis. The composition of such metabolites differ with different types of plant, plant part, and the protocol followed for the preparation of extract [176].

7. Conclusion

This chapter summarizes the fundamental introduction of NMs and NPs, the significance of colloidal metal NPs for range of applications, diverse physicochemical and biological pathways for synthesis of colloidal NPs and the parameters affecting the synthesis of NPs. Colloidal metal NPs, notably noble metal NPs such as gold, are being utilized since ancient times for multiple applications due to eminent and unique properties which make them superior compared with molecules or fellow bulk materials. Further, these NPs are preferred for biomedical applications due to their effectiveness to attenuate the shortcomings of traditional provisions, as it can be manipulated to deal healthily with the *in vivo* biological environment. Alongside,

the size of NPs compliments them with access through cells and tissues which helps not only to diagnose the disease proficiently but also aids for site specific treatment. Such prospective usages encourage the production of NPs in massive quantity. The colloidal metal NPs have been synthesized dominantly by using chemical and physical methods for many years, but the shortfalls of the methods confine their practice in biological fields. Hence researchers have opted a biological friendly way to synthesize NPs from natural environmental sources. Even though the mechanism of green production of NPs from microorganisms and plants is not yet entirely revealed, the synthesizing parameters, namely pH, temperature, time, concentration of metal salt affect the synthesis of NPs to a great extent and their optimization is very much necessary to yield the NPs in bulk quantity with desired properties. Besides the ongoing research on colloidal metal NPs from last few decades, its actual implementation in clinical field is at primary stage and many aspects such as distribution of NPs inside body, their accumulation and clearance from the body after treatment etc. need to be addressed for better involvement of NPs in biomedical applications.

Conflict of interest

All the authors declare that there is no conflict of interest.

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