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REVIEW

Synthesis methods of functionalized nanoparticles: a review

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Abstract
With the recent advancement in nanotechnology, nanoparticles (NPs) offer an ample variety of smart functions than conventional materials in various aspects. As compared to larger particles, NPs possess unique characteristics and excellent abilities, such as low toxicity, chemical stability, surface functionality, and biocompatibility. These advantageous properties allow them to be widely utilized in many applications, including biomedical applications, energy applications, IT applications, and industrial applications. In order to fulfill the increasing demands of NP applications, existing NP synthesis methods need to be improved based on the requirements of different applications to further their usage. A comprehensive understanding of the relationships between synthesis parameters and properties of NPs can help us better fine-tune them with designed properties and minimal toxicity. This review paper will discuss the commonly used synthesis methods of functionalized NPs, as well as future directions and challenges to develop various synthesis methods further.

Keywords Nanoparticles · Single synthesis methods · Biosynthesis methods · Combined synthesis methods · Processing parameters

Introduction

In the past decades, multiple types of NPs have gained tremendous interest in various applications due to their unique physicochemical and mechanical properties. Metallic NPs such as silver (Ag) NPs can be applied in the healthcare sector, electronic products, or environmental applications [1, 2], or gold (Au) NPs can be used in probes, diagnostic, and sensors due to the optical and electronic properties [3], or superparamagnetic iron oxide NPs (SPIONs) that can serve as contrast agents for different imaging applications [4]. Ceramic NPs such as hydroxyapatite NPs (HAp) have been extensively used in electronics or tissue engineering [5], or mesoporous bioactive glass NPs can be used to deliver bioactive molecules in a sustained and targeted drug release manner [6]. Polymeric NPs like poly(lactic-co-glycolic acid) (PLGA) NPs [7] or polylactic acid (PLA) NPs [8] are extensively researched for their drug delivery functions.

In order to explore more types of NPs for various applications, diverse synthesis methods have been developed to produce high-quality NPs with consistency, such as dry methods, wet methods, high-temperature synthesis methods, biosynthesis, and combination synthesis methods. Each method can be further categorized into multiple sub-methods. However, each sub-method has its benefits and shortcomings when it comes to the characteristics of NPs, manufacturing speed, cost, feasibility, and environmental impact. Different synthesis methods have a significant impact on the characteristics of NPs, such as microstructure, morphology, stoichiometry, crystallographic structure, and phase purity [9, 10].

These novel nanomaterials can bring us huge benefits and new research opportunities in various sectors. However, NPs may be harmful to humans, animals, and the environment. In biomedical applications, the potential cytotoxicity and genotoxicity of NPs may induce unwanted damages to the host [11]. Reports mention that NPs can enter nearby cells or tissues and causing systemic reactions and toxicities [12, 13]. Besides, reactive oxygen species (ROS) can be produced under environmental stress, like UV, heat, or foreign objects. As a product of cell metabolism, ROS and its associated prod-

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ucts like hydroxyl radicals play a vital role in NP-induced toxicity [14]. Multiple parameters of NPs, like size, morphology, surface chemistry, dosage, purity, composition, stability over time, uptake, dosimetry, and aggregation level can affect their toxicity [15]. NPs possess hazardous effects on the environment as well, such as water or soil. The status of NPs in water or soil, such as toxicity, dissolution, and agglomeration, can affect the overall environment, and the animals live in it [16].

Future applications require NPs to serve multiple functions but with minimal side effects and affordable cost. The existing standard synthesis methods cannot fulfill all the increasing demands. As such, advanced synthesis methods should precisely and comprehensively control all the processing parameters to obtain NPs with predesigned properties. In this review, we mainly focus on the recent advances in functionalized NP synthesis methods, together with current challenges and future directions of further developing synthesis methods.

Single synthesis methods of NPs

During the past decades, various synthesis methods have been developed to prepare NPs. Processing parameters and conditions can vary significantly among different synthesis methods. Single synthesis methods are simple and straightforward as compared to combinational methods, but they are often also associated with their limitations. In this section, the commonly used single synthesis methods of NPs are described below.

Dry methods

As the name suggests, there is no solvent needed during dry methods. The characteristics of NPs produced by dry methods are not affected by the processing parameters profoundly. Thus, dry methods are perfect for the mass production of NPs without precision control [9]. Dry methods contain the following methods: solid-state synthesis method [17, 18], mechanochemical synthesis method [19–21], and inert gas condensation synthesis method [22–24].

Solid-state synthesis method

Solid-state synthesis method is a reaction among the dry raw materials induced by thermal treatments to expedite the reaction since the solids can hardly react at room temperature [25]. It can be used in mass production of particles due to its relatively simple procedure. The solid-state synthesis is a relatively simple, eco-friendly, and economical method [26]. A standard solid-state synthesis method is shown in Fig. 1. The final quality of NPs produced can be affected by processing parameters like reaction time, reaction pressure, reaction atmosphere, and cooling speed. Solid-state synthesis method can be significantly accelerated under microwave-assisted (MW-assisted) conditions due to its rapid heating, selective coupling, and upgraded reaction kinetics [27]. The main issue of solid-state synthesis method tends to produce microparticles but not NPs, and particles often come with irregular shapes.

Hussein et al. [18] synthesized pure zinc oxide (ZnO) NPs with a one-step solid-state synthesis method. First, gum arabic (GA) was mixed with sodium hydroxide (NaOH) powder to generate alkali-treated GA, followed by adding in zinc acetate dihydrate to produce zinc hydroxide ($Zn(OH)_2$) through grinding. The solid mixture was washed several times to remove the excess NaOH and GA. Finally, the mixture was dried and calcined at 600 °C to turn $Zn(OH)_2$ to ZnO NPs [18]. This solid-state synthesis method came with several advantages, such as a simple one-step reaction, no toxic reagents required, large-scale production possibility, and minimal waste [18]. ZnO NPs can be utilized in drug delivery due to its high cytocompatibility and relatively large surface area [18], or food packing applications due to its antimicrobial activity [28], or UV filters used in cosmetic products for their effectiveness and safety [29].

Mechanochemical synthesis method

Mechanochemical synthesis method does not require heat to create a chemical reaction, but high-energy mechanical activation (usually by ball milling) to induce the chemical changes to fabricate advanced materials, such as nanocrystalline alloys and ceramics on large scales [30]. Mechanochemical synthesis method has gained special attention in ceramic NP manufacturing for various applications, including electronics, food packing, biomedical sector. As compared to solid-state synthesis method, mechanochemical synthesis method is more straightforward and able to produce NPs with more well-defined structures [9]. The primary deficiency for mechanochemical synthesis method is the low phase purity of NPs. Both solid-state and mechanochemical synthesis methods are easy to cause aggregation in large-scale production [31]. However, adding salt matrix in the process can minimize the aggregation problem in mechanochemical synthesis, in which the salt matrix can be removed through washing before final calcination [28].

For processes with ball milling involved, such as mechanochemical synthesis method or hydrothermal–mechanochemical synthesis method, processing parameters such as processing temperature and time, material type; milling ball size, number, geometry, and momentum; respective volumetric ratios; and weight ratio of ball and powder can affect the quality of the final product. Generally, higher heat treatment temperature can increase

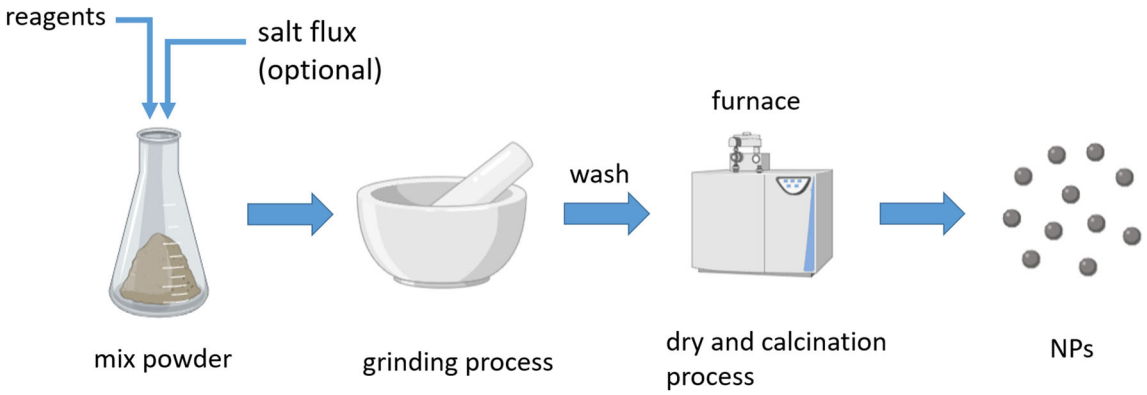

Fig. 1 A schematic process of a standard solid-state synthesis method

the size of the NPs, while longer milling time can significantly decrease the size [28]. A comprehensive study can help us to understand better the relationships between synthesis parameters and properties of NPs.

Mechanochemical synthesis method was used by Hattori's team to produce zinc-doped calcium phosphate (Zn-CaP) for controlled zinc release [20]. The powder sample contained calcium oxide/dicalcium phosphate/ZnO (CaO/CaHPO4/ZnO) with specific molar ratio was grounded in a ball mill with purified water added in later, and the ground preparation was heated up to 800 °C for 5 h to obtain the final product [20]. As compared to conventional high heat synthesis of Zn-CaP, it required a higher temperature and longer processing time. This method could produce these NPs on a large scale in an energy-saving way. More importantly, the team found out Zn-CaP can release zinc ions in a consistent and sustained way to help bone healing, which is a promising bone grafting material [20].

Inert gas condensation synthesis method

Inert gas condensation synthesis method [22] is extensively applied in metallic NP fabrication. An ultrahigh vacuum chamber is filled with inert gas to maintain a very high pressure to evaporate metals. Through countless collisions with the gas atoms, the evaporated metal atoms lose their kinetic energy and therefore slow down and condense into particles. Because of Brownian coagulation, these particles can grow, coalesce, and form NPs as final products [23]. As one of the essential elements in humans, magnesium (Mg) serves important functions, and Mg is a promising biodegradable material for various biomedical applications [24]. Wen et al. [22] fabricated magnesium (Mg) NPs through inner gas condensation. In the Mg NP production, Mg was evaporated into gas form by induction heating, and then, Mg vapor was cooled by argon gas to form Mg NPs [22]. Both the experiments exhibited Mg NPs with controllable size and size distribution. The particle size could be adjusted by controlling the inert gas pressure, temperature, and flow rate. Higher pressure and lower temperature could result in larger size particles and wide size distribution [22]. Moreover, NPs generated under higher pressure showed increased crystallization and higher magnetization, which can be utilized as magnetic NPs.

Even though inert gas condensation synthesis method produces NPs with excellent quality control, the production rate is exceptionally slow. For most metallic NPs, the production rates can be as low as 1 g/day, while it can be slightly higher (20 g/day) for particular metallic oxide NPs [23]. This drawback limits its application to industrial production. Further research should be done to enhance the production rate to expand the usage of this synthesis method in different sectors.

Wet methods

Unlike dry methods, where the particles generated are usually irregular in shape and large in size. The wet methods can precisely control the morphology and the average size of NPs, which makes them the ideal synthesis methods for NP production in many applications [9]. However, wet methods do not have complete control over the crystallinity and phase purity of NPs, and they are relatively expensive and time-consuming processes. In general, wet methods of NPs preparation have four commonly used sub-types as described below.

Chemical precipitation synthesis method

Chemical precipitation synthesis method [32] changes the form of materials dissolved in the solvent into solid particles. It is the most straightforward route for NPs produced on a large scale, and low cost among all the wet methods. Chemical precipitation synthesis method can produce both microparticles, and NPs at low temperatures depend on the salts used [33]. The salts refer to the inorganic metal salts

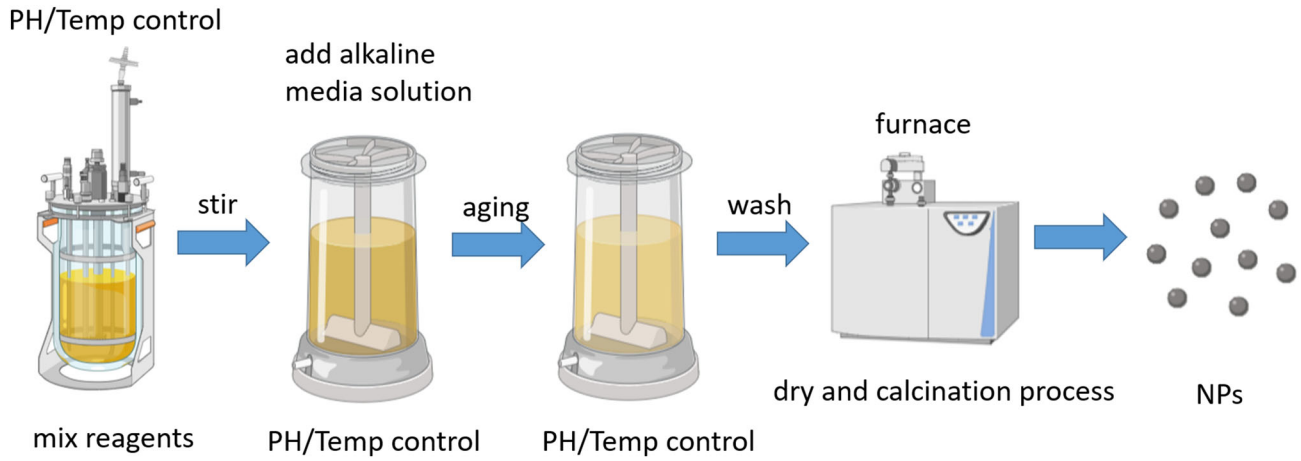

Fig. 2 A schematic process of a standard chemical precipitation synthesis method

such as nitride and chloride which are dissolved in water. A standard process of chemical precipitation synthesis method is shown in Fig. 2. Multiple parameters such as temperature, PH value, solvent type, mixing rate of solvent and reagent, and post-treatment may affect the characteristics of the final NPs produced. Therefore, the size of the particles is not easy to control, and the particles usually come with a wide size distribution [9].

Frasnelli et al. [34] used an aqueous precipitation synthesis method to produce strontium-substituted HAp (Sr-HAp) NPs in a well-controlled nitrogen (N_2) atmosphere. They dissolved the appropriate amounts of calcium nitrate tetrahydrate ($Ca(NO_3)_2{\cdot}4H_2O$), diammonium phosphate ($(NH4)_2HPO_4$), and strontium nitrate ($Sr(NO_3)_2$) to make Ca + Sr nitrate solutions and the phosphate solutions, then added phosphate solution into nitrate solution and stirred in N_2 condition, followed by a series of post-treatment to obtain the Sr-HAp NPs [34]. Strontium content in the final product could be adjusted through changing the relative amount of $Ca(NO_3)_2{\cdot}4H_2O$ and $Sr(NO_3)_2$ in the nitrate solution [34]. The promising results indicated that Sr-HA NPs could transport Sr to the targeted bone area and promote bone regeneration [34]. Tantalum pentoxide (Ta_2O_5) NPs could be produced with precipitation synthesis methods and coated with poly(acrylic acid) (PAA) for better drug loading efficiency with methotrexate for controlled drug release applications [35]. Different thicknesses of PAA layer on Ta_2O_5 NPs could be formed through adjusting the polymerization time [35]. PAA- Ta_2O_5 nanocomposites with drug delivery and cell imaging functions have huge potential in biomedical applications.

Solvent displacement synthesis method can produce polymeric NPs loaded with bioactive molecules dedicatedly. It is a method based on precipitation with subsequently volatile solvent eliminated to harden the polymer. A mixture of polymer, drug, and hydrophobic surfactant is precipitated in the solvent containing organic solution with saturated aqueous solution added in later [36]. Polymeric NPs loaded with drugs can be materialized after solvent diffusion into water rapidly, which is due to the decrease in interfacial tension after the organic solution and aqueous solution reaction [37]. The solvent is removed from the suspension later, followed by centrifuge and lyophilize to obtain the final product. Wang et al. [38] implemented a water-miscible solvent displacement method to fabricate cationic polymeric (bis(poly(lactic-co-glycolic acid)-phenylalanine-polyethylene glycol)-quaternary ammonium grafted diethyl triamine) NPs (BPPD) loaded with simvastatin (SIM). The team added distilled water into each solution to precipitate NPs through solvent displacement synthesis method to find out which solvent solution can generate the smallest particle [38]. BPPD obtained could be an excellent drug carrier, such as loaded with SIM to enhance osteoblast activity and increase osteogenesis with BMSCs [38], or loaded with plasmid DNA for potent gene transfection due to fast cell penetration ability [39].

Sol–gel synthesis method

Sol–gel synthesis method [40–42] is one of the most popular methods in NP preparation. Sol–gel technique offers many biomaterials with predefined properties in a relatively simple way, but the cost is higher as compared to other wet methods, and a particular reagent is required [43]. Sol–gel synthesis method is based on the inorganic polymerization of metal alkoxides [44]. A sol (a colloidal suspension of nanosized particles) is created by the addition of a surfactant, followed by condensation and gelation reactions [44]. During the process, the sol is converted into gel. Then, the gel is dried and converted into precipitate, which can be calcinated to obtain the final product. Figure 3 gives a general idea of the standard sol–gel synthesis method. Processing parameters, such as PH

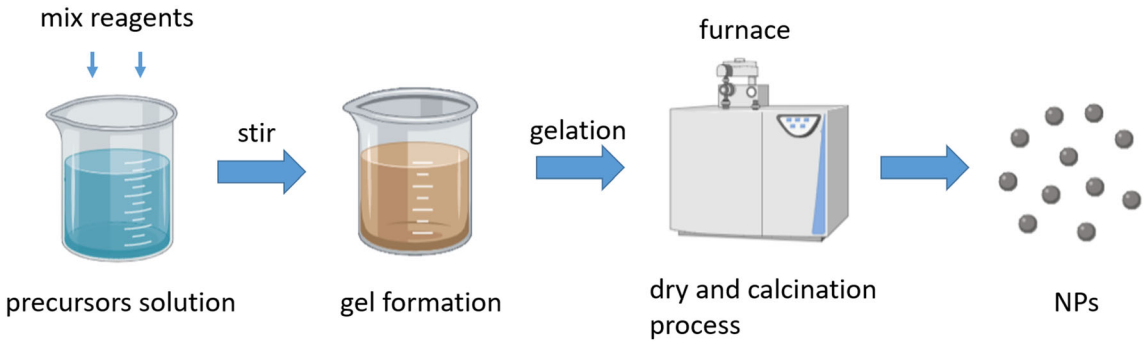

Fig. 3 A schematic process of a standard sol–gel synthesis method

value, stirring speed/duration, reaction temperature/time, can affect the porosity, microstructure, crystallinity, and densification of the final product. The substantial features of the sol–gel method are high purity, superior homogeneity, lower processing temperature, excellent size, morphological control, and uniform phase distribution in the multi-component system [45]. The sol–gel process can generate ultrafine or spherical-shaped NPs, especially ceramic NPs [46]. Faure et al. [47] demonstrated that instead of using a high concentration of nitric acid solution in the traditional process, high bioactive glass powders could be produced by sol–gel synthesis method with a very low concentration of a citric acid solution to reduce the cost and process time, while bioactive glass powders can be used as bone substitutes in tissue engineering. Dubey et al. [48] used tetraethyl orthosilicate (TEOS) as a precursor to fabricate silica NPs for many industrial applications; the size and shape of silica NPs were controllable through adjusting the amount of surfactants and TEOS. Qi et al. [49] used sol–gel synthesis method to produce monodisperse magnetite (Fe_3O_4) NPs with high purity. SPION, like Fe_3O_4 NPs, served multiple functions in theragnostic application [50], drug delivery [51], and bioimaging [52].

In particular, the Stöber process is often known as a special sol–gel method to prepare controllable and uniform size silica NPs to enhance the mechanical strength of the scaffold [53–55]. Roopavath et al. [54] found out that the biocompatibility and osteogenic ability of the hydrogels are significantly built up with silica NPs added into hydrogel scaffolding. Silica NPs can be added into the hydrogel to increase its viscosity and printability of the scaffolds. In order to overcome the low mechanical strength of the scaffold, Chen et al. [42] developed a modified sol–gel process to fabricate sodium oxide-containing bioactive glass ceramics, which the structures showed improved mechanical strength, without losing biodegradability.

Hydrothermal synthesis method

Unlike chemical precipitation synthesis method and sol–gel synthesis method that reacts at standard temperature and pressure, hydrothermal synthesis method deals with high temperature and pressure at the aging step, which requires more expensive equipment [56, 57]. Hydrothermal synthesis method is to crystallize substances using the aqueous solution at high temperature and high vapor pressure; thus, most materials can be soluble in a proper solvent through particular heat and pressure [23]. It can produce high crystalline NPs with well-defined size and morphologies through controlling critical factors such as reaction temperature/time, organic additive, solvent effects, and mineralizer concentration [58]. Hydrothermal synthesis method takes place in a closed container like an autoclave; thus, it is not easy to observe the reaction in real time. Nevertheless, the reaction rate is relatively slow. Therefore, ultrasonic, electric field, or microwaves are often used together to expedite the manufacturing process.

Despite its limitations, hydrothermal synthesis method can still draw much attention due to its easiness and adequate control of the products. Geng et al. [56] implemented a one-step hydrothermal synthesis method to produce Ag/strontium (Sr) incorporated HAp NPs. First, $Ca(NO_3)_2{\cdot}4H_2O$, silver nitrate ($AgNO_3$), $Sr(NO_3)_2$, and trisodium phosphate (Na_3PO_4) were used as calcium (Ca), Ag, Sr, and phosphorus (P) precursors [56]. $Ca(NO_3)_2{\cdot}4H_2O$ was added into Na_3PO_4 solution and then heated together. The precipitates were washed, dehydrated, and then dried. The dried powder was manually ground using a corundum mortar to generate the HAp NPs [56]. $AgNO_3$ or $Sr(NO_3)_2$ was used to replace $Ca(NO_3)_2{\cdot}4H_2O$ to generate Ag-HAp, Sr-HAp, and Ag-Sr-HAp NPs, respectively, to gain a comprehensive understanding on the effect of Ag and Sr ions [56]. While Ag ions were beneficial in antimicrobial area, but the toxic of Ag ions could harm osteoblasts [56]. As a binary element, Sr could help with osteoblast proliferation to a certain extent. The biocompatibility of Ag-Sr-HAp can be further improved

through adjusting Ag and Sr composition to achieve a balance status. Further research should be carried out to optimize the composition of the Ag-Sr-HAp nanocomposite.

Emulsion synthesis method

Emulsion synthesis method [59, 60] has precision control of the size and size distribution of the NPs, but it is usually expensive due to large amounts of surfactants, and organic solvents are needed. Processing parameters involve stirring speed/duration, type of surfactant/cosurfactant, and ratios of water/oil. Surfactants, such as cetyltrimethylammonium chloride (CTAC) and sodium dodecyl sulfate (SDS), can be added to the emulsion to carry out the reaction on a small scale [9]. Typically, emulsion synthesis method refers to the presence of oil as the external phase and water as the internal phase, while invert emulsion usually refers to the presence of water as the external phase and oil as the internal phase [61, 62]. The desired NPs can be generated after the mixing, reaction, filtration, washing, freeze-drying, and post-treatment.

As the major mineral constituent of human bone, HAp possesses not only excellent biocompatibility and bioactivity, but also easy to be produced through most of the standard synthesis methods. Ma et al. [62] fabricated spherical HAp NPs with satisfactory uniformity and regularity through inverse microemulsion synthesis method. The oil solution was formed by mix n-amyl alcohol and Span-80 into cyclohexane, and then, calcium nitrate ($Ca(NO_3)_2$) solution and $(NH_4)_2HPO_4$ solution were added dropwise into the oil solution under ultrasonic environment to get Ca microemulsion and P microemulsion, respectively [62]. Then, these two microemulsions were mixed and agitated for different hours [62]. A series of post-treatment included filtration, washing, freeze-drying, and grinding was performed on the precipitants [62]. The organic molecules were removed from precipitants through sintering to obtain the final pure HAp NPs [62]. Various parameters, such as reaction temperature and time, can affect the quality of HAp NPs. The team managed to identify further that the size and morphology of HAp can be affected by the microemulsion droplets' thermodynamic stability [62].

High-temperature synthesis methods

High-temperature synthesis methods contain three basic synthesis methods generally: combustion synthesis method [63–65], pyrolysis synthesis method [66, 67], and spray drying and flame spray synthesis method [68–70]. High-temperature processes usually deal with an elevated temperature, which is high energy consumption. Besides, high-temperature processes lack proper control over the processing variables, and the generation of the secondary aggregates may be the main downside. However, the low-cost and straightforward preparation processes are still determining factors, especially in industry sectors.

Combustion synthesis method

The basis of combustion synthesis method comes from thermochemical concepts applied in propellants and explosives chemistry [71]. Ceramics, composites, alloys, and intermetallics can be prepared through this synthesis method. Parameters such as ignition temperature, actual combustion flame temperature, synthesis time, and reactant mixture can all affect the properties of NPs produced [58]. It is heavily used in industry due to the low cost, affordable raw materials, easy preparation process, and homogeneity of NPs. However, the wide size distribution and severe aggregation have also limited its usage in specific applications [9].

Pyrolysis synthesis method

Pyrolysis synthesis method decomposes organic materials chemically, which usually happens at high temperatures and inert atmosphere. The thermal decomposition leads to new molecules formation and therefore synthesizes NPs. The treated material composition, process temperature, residence time will all affect the pyrolysis synthesis outcome. Specific post-treatments at high temperatures may be required to achieve a high crystalline product [9]. NPs fabricated directly by this rapid pyrolysis-based method is homogeneous and highly crystalline, but similar to combustion synthesis method, it also has drawbacks, such as wide size distribution, severe aggregation, and high energy consumption.

Spray drying and flame spray synthesis methods

Spray drying synthesis method typically uses hot gas in the chamber to rapidly dry the solvent to produce dry particles. The size of the particle is very consistent, which makes this method very popular among specific industries. Flame spray synthesis method [72] injects assorted types of low-cost metal oxides precursors into the flame to produce homogeneous NPs with high purity and relatively narrow size distribution. There is a wide variety of low-cost precursors, such as titanium dioxide (TiO_2) or silica to choose [72]. The precursor concentration, flame temperature, and the residence time will all influence the morphology of NPs. Strobel et al. [73] used flame spray synthesis method to fabricate bioactive glass NPs. The team used a series of metal precursors of silicon (Si) from hexamethyldisiloxane, sodium (Na) from sodium hydroxide, P from tributylphosphate, potassium (K) from potassium bicarbonate, Mg from magnesium oxide, Ca from calcium hydroxide, and Sr from strontium acetate and diluted with xylene solution [73]. The mixed solution

was ignited inside the chamber to burn all the precursors to obtain the bioactive glass NPs [73].

As compared to wet methods, dry methods and high-temperature synthesis method have fewer applications due to the quality and quantity of the NPs produced which may not meet the high standard of nowadays. Future research is needed to further utilize these methods. The features of commonly used single synthesis methods for NPs are shown in Table 1.

Biosynthesis methods of NPs

Biosynthesis methods have attractive features in NP production, such as low-cost approaches, eco-friendly solvents, abundant availability, renewable materials, non-toxic, and clean chemicals [74]. Different biomaterials, such as bacteria [75–78], fungi [79, 80], algae [81, 82], yeast [83, 84], plant extracts [85–89], and even waste materials [90–92], have acted as eco-friendly and non-toxic precursors for the rapid synthesis of NPs with various applications. More importantly, NPs produced from biosynthesis methods generally possess enhanced biocompatibility as compared to traditional synthesis methods [93]. Table 2 lists the commonly employed materials of NP biosynthesis.

Microorganism biosynthesis

Microorganisms, such as bacteria, fungi, algae, and yeast, have enormous potential in NPs synthesis. Because of their enzymes, microorganisms can accumulate and process toxic metal ions into stable metal NPs. In general, NPs can be produced extracellularly or intracellularly in microorganisms [80]. Extracellular synthesis is more commonly used due to its less complicated than intracellular synthesis. In extracellular synthesis, after culturing the microorganisms, biomass is removed through centrifugation. The supernatant of microorganisms is used to mix with the metal salt solution for incubation. The whole biosynthesis process can be closely monitored by observing the change in the color of the culture medium [93]. The final NPs can be obtained through a series of post-treatment including centrifugation, washing, drying, and collection, while for intracellular synthesis, the biomass of microorganisms is collected through centrifugation and then dissolved with the metal salt solution for incubation [93]. The reaction process can be monitored in real time as well. There are a few additional steps after the incubation to remove the biomass, such as mechanical disruption or ultrasonication, washing, and centrifugation. These additional steps can break the cell wall and release the NPs inside them [93]. Final NPs can be collected after the same post-treatment. As compared to intracellular synthesis, extracellular synthesis is more accessible, but the residual fermentation media may affect the reaction and the yield of NPs. At the same time, additional extraction and purification steps are needed for intracellular synthesis, which may affect the final quality and quantity of NPs.

For biosynthesis of NPs, a few critical processing parameters need to be controlled precisely to avoid the polydispersity of NPs. Temperature is the first key parameter. It should be kept at the highest temperature possible since the enzyme responsible for NP production is more active at higher temperatures [93]. PH level is the second key parameter because different sizes, shapes, and quantities of NPs can be synthesized at different PH levels [94]. Incubation time plays an essential role in the quality of NPs as well. Too long or too short of incubation time may cause agglomeration of NPs in many cases [84]. Other essential processing parameters like oxygen supply, mixing ratio, aeration, metal solution concentration can affect the yield and quality of NPs produced. All these parameters need to be optimized to obtain a stable system to synthesize NPs.

In the early development of biosynthesis, bacteria were the first microorganisms used due to its easiness, eco-friendly, and potential large-scale production. It is the most well-established biosynthesis method. Many bacteria like *Escherichia coli*, *Bacillus subtilis, Veillonella atypica, Cupriavidus metallidurans, Streptomyces bikiniensis, Shewanella oneidensis, Aspergillus terreus,* and *Rhodopseudomonas capsulate* have been explored to produce various NPs, in which microorganisms react with and metal ions chemically reduce them into biologically stable NPs [75–77]. Various parameters can affect the growth of NPs: PH, oxygen supply, temperature, and incubation time. Ahmad et al. [76] synthesized selenium (Se) NPs with *Streptomyces bikiniensis*, and the Se NPs produced exhibited stability, bioefficacy, and eco-friendly. He et al. [78] used *Rhodopseudomonas capsulate* to produce Au NPs with various shapes and sizes. With proper control of PH value, Au NPs with size ranged from 10 to 20 nm could be synthesized.

Fungi can produce NPs more efficiently as compared to other biosynthesis methods due to their tolerance and bioaccumulation ability [95, 96]. NPs produced extracellularly are generally smaller than intracellularly, and therefore, most of the studies are carried out extracellularly. Molnár et al. [80] utilized 29 thermophilic filamentous fungal strains to synthesize Au NPs with three different low-cost and straightforward approaches: extracellular extract method, autolysate method, and intracellular extract method. The authors have thoroughly investigated how the characteristics and quality of Au NPs were affected by the supernatant of the fermented fungi, or the autolysate of fungi, or the intracellular extract from the mechanically disrupted cells. Figure 4 shows the main steps of each method, where PDB stands for potato dextrose broth. It can be seen that extracellular synthesis is the easiest among the three methods. Each method also

Table 1 Features of single synthesis methods of functionalized NPs

Synthesis methods	Advantages	Disadvantages	Main processing parameters	Characteristics of particles				
				Size	Size distribution	Shape	Crystallinity degree	Phase purity
Solid-state synthesis method	Low cost, large scale, simple to produce, eco-friendly	Severe aggregation, wide size distribution, high temperature required, slow reaction	Reaction time, reaction pressure, reaction atmosphere, and cooling speed	Usually micron	Wide	Diverse (usually irregular)	Very high	Low
Mechanochemical synthesis method	Low cost, large scale, simple and efficient	Severe aggregation, wide size distribution, high energy consumption, long milling time, potential contamination of NPs due to metal balls	Processing temperature and time, material type; milling ball size, number, geometry, and momentum; milling media; rotational speed; respective volumetric ratios; weight ratio of ball and powder	Micron to nano	Wide	Diverse	Very high	Low
Inert gas condensation synthesis method	Precise control of particle size and size distribution	High cost due to equipment, extremely slow rate, laboratory-scale only	Inert gas type, pressure, temperature, flow rate	Nano	Narrow	Diverse	Various	Various
Chemical precipitation synthesis method	Low cost, large scale, low temperature, energy saving, solvent-free, simple, and rapid preparation	Aggregation, product size not easy to control, wide size distribution, time-consuming, may use harsh chemical and cause residual toxic	Temperature, PH value, solvent type, mixing rate of solvent and reagent, post-treatment	Micron to nano	Wide	Diverse	Low	Various
Sol–gel synthesis method	Narrow size distribution, precise size and morphology control, controllable degree of porosity, high purity	High cost, special reagents required, time-consuming, small scale, solvents may be harmful, particle agglomeration at certain cases	PH value, stirring time, synthesis temperature/time, solvent amount, the concentration of chemicals	Nano	Narrow	Diverse	Usually low	High

Table 1 continued

Synthesis methods	Advantages	Disadvantages	Main processing parameters	Characteristics of particles				
				Size	Size distribution	Shape	Crystallinity degree	Phase purity
Hydrothermal synthesis method	High crystallinity, precise control of size and shape, most materials are soluble at high temperature	High cost (autoclaves), impossible to observe the reaction process, potential safety issues, difficult to control the process, low reliability	Reaction temperature/time, organic additive, solvent effects, and mineralizer concentration	Micron to nano	Narrow	Needle, rod, octahedral	High	High
Emulsion synthesis method	Narrow size distribution, easy preparation, minimal agglomeration, precise control of size and shape, thermodynamically stable	High cost, time-consuming, requires a large amount of surfactant and/or cosurfactant, external factors (PH or temperature) affect the stability of the process	Stirring speed/duration, type of surfactant/cosurfactant, ratios of water/oil	Nano	Narrow	Needle, rod	Usually low	Various
Combustion synthesis method	Simple preparation process, homogeneity of products, low cost	High energy consumption, severe aggregation, wide size distribution	Ignition temperature, actual combustion flame temperature, synthesis time, reactant mixture	Micron to nano	Wide	Diverse (usually irregular)	Various	Usually high
Pyrolysis synthesis method	Low cost (wide variety of possible low-cost precursors), high crystallinity, high purity of materials, and size control	High energy consumption, severe aggregation	Material composition, process temperature, residence time, particle size, and physical structure of the particle	Micron to nano	Relatively low	Diverse	High	Various
Spray drying and flame spray synthesis method	Large scale, relatively low size distribution, high purity	High energy consumption, wide size distribution	Precursor concentration, flame temperature, and residence time	Micron to nano	Wide	Diverse can be cubic	Various	High

Table 2 Typical materials used in biosynthesis method

Category	Biomaterials	NPs	Brief processing method	Properties of NPs produced	Remarks	References
Bacteria	*Bacillus brevis*	Ag	Extracellular synthesis	Range from 41 to 68 nm, spherical shape, antibacterial ability	Potential antibacterial ability against multi-drug-resistant pathogens like *salmonella typhi* and *Staphylococcus aureus*	[75]
	Streptomyces bikiniensis	Se	Extracellular synthesis	Average particle size 17 nm, anticancer activity, stability, bioefficacy, eco-friendly show anticancer activity against Hep-G2 and MCF-7 cancers cells while maintaining neutral on normal cells	A few parameters can affect the yield and purity of NPs produced: precursor salt, carbon, and nitrogen source, PH, and oxygen; possible for large-scale production	[76]
Fungi	*Thermophilic filamentous fungi*	Au	Extracellular extract, autolysate, or intracellular extract (Fig. 4)	Range from 6 to 40 nm, small size distribution, drug delivery, and cell imaging functions	Filamentous fungi can produce Au, Ag, Fe_3O_4, or biometallic NPs	[80]
	Trichoderma reesei	Ag	Intracellular synthesis	Antibacterial ability, range from 5 to 50 nm	Large scale availability, biologically safe, low cost	[79]
Algae	*Cyanobacterial and green algae*	Ag	Intracellular synthesis	diverse shape (elongated, irregular, spherical), antibacterial ability	Ag NPs produced from one strain show no antibacterial ability, probably due to large size (around 80-100 nm in diameters)	[81]
	Bifurcaria bifurcata	CuO	extracellular synthesis	size ranging from 5-45 nm, antimicrobial ability	various applications, eco-friendly	[101]
	Sargassum muticum	Fe_3O_4	Extracellular synthesis	Cubic shape with an average size 18 ± 4 nm, stronger antimicrobial ability than NPs synthesized by traditional chemical methods	Can be extended to other metal oxide synthesis	[99]
Yeast	*Cornitermes cumulans*	Ag/AgCl	Extracellular synthesis	Antibacterial ability, circular shape with size ranging from 2-10 nm	Biosynthesized Ag/AgCl NPs show compatible functions and abilities with industrial synthesis	[83]

Table 2 continued

Category	Biomaterials	NPs	Brief processing method	Properties of NPs produced	Remarks	References
	Pichia kudriavzevii	ZnO	Extracellular synthesis	Antimicrobial and antioxidant abilities; NPs generated at 12 h exhibited agglomeration and low crystallinity with an average size of 10 ± 2.1 nm; NPs generated at 24 h showed hexagonal shape and high crystallinity with an average size of 32 ± 4.7 nm; NPs were later developed into irregular shapes and seriously agglomeration with an average size 59 ± 10.6 nm at 36 h	Incubation time can affect the quality of NPs the most; NPs generated at 24 h demonstrated the most acceptable quality among the three groups.	[84]
Plant extracts	Silk fibroin film	Ag	*In situ* synthesis from silk fibroin films containing $AgNO_3$ solution—exposed to light for incubation—post-treatment to collect Ag NPs formation	Antibacterial ability, spherical shape with 5-12 nm diameter, higher $AgNO_3$ concentration can generate smaller size Ag NPs	Ag NPs embedded films help with the proliferation of osteoblasts; can be used as coating on medical devices	[85]
	Cymbopogan citratus (lemongrass)	Al_2O_3	MW-assisted extracellular synthesis	Spherical shape with average size 34.5 nm, antibacterial ability against multi-drug-resistant *Pseudomonas aeruginosa*	Cost-effective, eco-friendly, non-toxic	[87]
	Plectranthus amboinicus	NiO	MW-assisted extracellular synthesis	Average size 820 nm, spherical shape, enhance apatite deposition which helps with bone-bonding and increase osteoconductivity	*Plectranthus amboinicus* is used as the reducing agent to produce NiO NPs; higher leaf extract concentration can reduce particle size	[89]
Waste materials	Grass waste	Ag	Extracellular synthesis	Most are spherical shape, average size 15 nm, antibacterial, anticancer, antifungal abilities	Waste grass extract is treated as both reducing and capping agents	[90]
	Waste corncob	Au, Ag	Extracellular synthesis	Ag: size ranging from 2-28 nm, average size 11 nm, spherical shape, antibacterial ability; Au: size ranging from 5-50 nm, average size 35 nm, multiple shapes	$AgNO_3$ solution and hydrogen tetrachloroaurate (III) hydrate ($HAuCl_4 \cdot 3H_2O$) are used as precursors for Ag/Au NP production, respectively	[91]

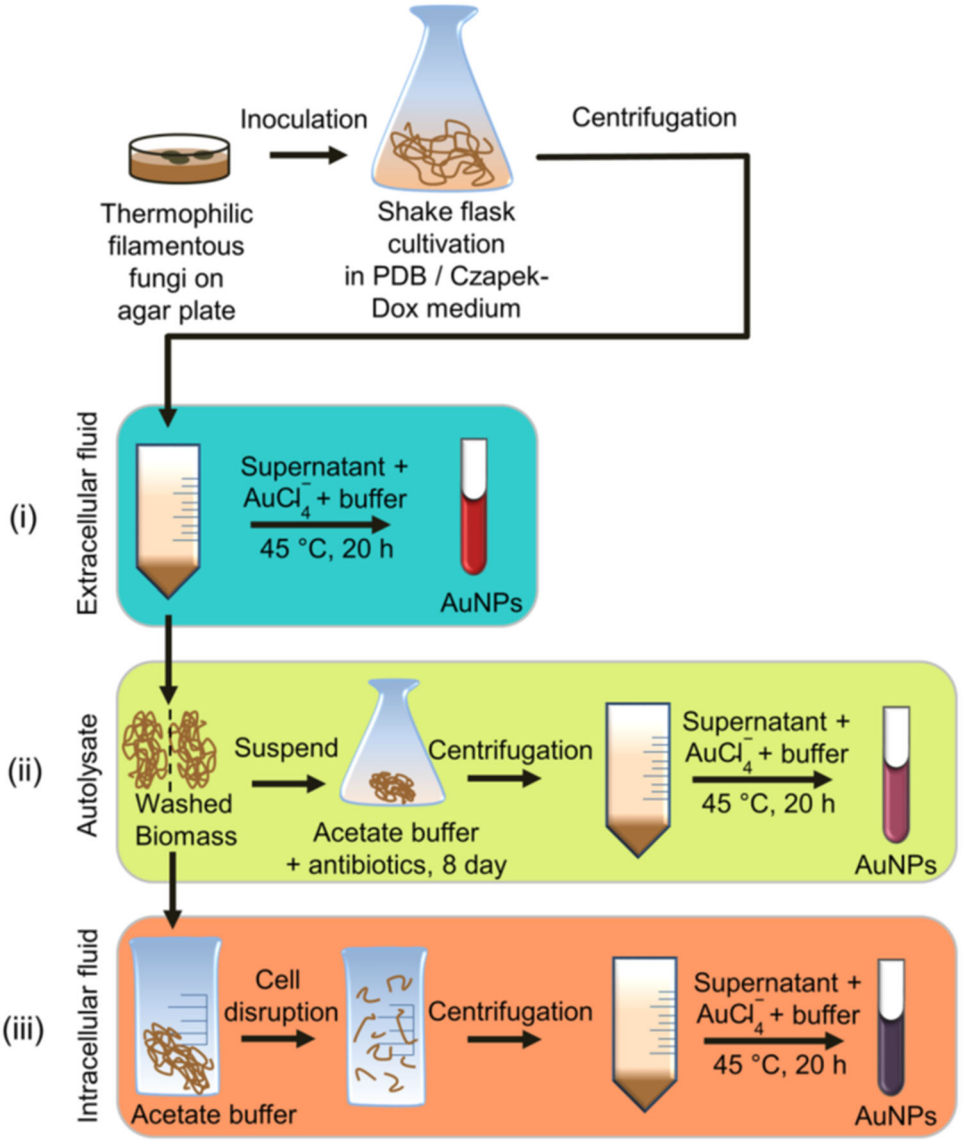

Fig. 4 A schematic shows different extracts from fungi preparation and three different Au NPs synthesis methods (i) extracellular extract method, (ii) autolysate method, and (iii) intracellular extract method. Copyright Nature group and reproduced with permission [80]

has its limitation: Residual fermentation media may affect the reaction for extracellular synthesis, potential bacterial contamination may occur during autolysate method, and additional extraction and purification steps are needed for intracellular synthesis.

Algae are one of the rich sources of biomolecules in aquatic organisms [97]. Same as other microorganisms, algae can act as reducing agents to synthesize NPs from metal salts solution without any toxic products produced. Au NPs [98], Ag NPs [81, 82], iron oxide (Fe_3O_4) NPs [99], ZnO NPs [100], and copper oxide (CuO) NPs [101] can be produced from algae-mediated biosynthesis. Uma Suganya et al. [98] synthesized stable and spherical shape Au NPs with blue green alga, and Au NPs exhibited strong antimicrobial ability against Gram-positive bacteria. Azizi et al. [100] used brown marine macroalga *Sargassum muticum* aqueous extract to produce ZnO NPs, and the NPs produced have hexagonal structures with size ranging from 3–57 nm. However, ZnO NPs were agglomerated together due to internal polarity and electrostatic attraction. The agglomeration could be improved with proper adjustment on the processing parameters [100].

The processing parameters of NPs produced from yeast are easy to control in laboratory conditions [102]. They can grow fast with limited nutrients and generate NPs in a rapid and cost-effective way. Eugenio et al. [83] used yeast (*Cornitermes cumulans*) to produce Ag and silver chloride (AgCl) NPs with extracellular synthesis. Both Ag and AgCl NPs produced were circular shape and size ranging from 2 to 10 nm and possessed strong antibacterial abilities [83]. Moghaddam et al. [84] synthesized ZnO NPs with *Pichia kudriavzevii* yeast strain with extracellular synthesis. The author mixed

zinc acetate dihydrate solution with fungal cell-free filtrate and incubated for different durations (12/24/36 h) to obtain ZnO NPs [84]. The author stated that the reaction time played a critical role in the size, shape, and size distribution of NPs generated [84]. NPs generated at 12 h exhibited agglomeration and low crystallinity, with an average size of 10 ± 2.1 nm; NPs generated at 24 h showed hexagonal shape and high crystallinity, with an average size of 32 ± 4.7 nm; NPs were later developed into irregular shapes and seriously agglomeration, with an average size of 59 ± 10.6 nm at 36 h [84]. NPs generated at 24 h demonstrated the most acceptable quality among the three groups. The strong antimicrobial and antioxidant abilities of ZnO NPs made them extremely useful in bone-related applications. Yeast-mediated biosynthesis is also one of the least used among the biosynthesis mentioned above, possibly due to limited yeast available for NPs synthesis. Future exploration can expand the application of yeast-mediated biosynthesis.

The commonly used microorganisms, such as bacteria, fungi, algae, and yeast, are essential nano-factories that synthesize biocompatible, stable, and non-toxic NPs in an eco-friendly and cost-effective way. Other microorganisms, such as actinomycetes [103] or virus [104, 105], have also been explored by researchers, even though they are at very early developing stages and their applications are relatively limited. However, most microorganisms synthesis methods are slow and less stable as compared to other synthesis methods [96]. The uncertainties and complicated steps involved in handling the growth of microorganisms also limited their repeatability and consistency.

Plant extract biosynthesis

NPs derived from plant extract are suitable for the high demand of various applications. The biosynthesis of Ag NPs using plant extract is straightforward, efficient, cost-effective, and eco-friendly [86]. Patil et al. [85] in situ synthesized Ag NPs silk fibroin film and showed improved antibacterial ability (Fig. 5). Patil et al. [86] produced Ag NPs through *Madhuca longifolia* flower extract. $AgNO_3$ solution was mixed with flower extract and stirred for 20 min; Ag NPs were collected after the reaction and post-treatment [86]. NPs produced were perfectly shaped and displayed significant antibacterial activity against both Gram-positive (*B. cereus, S. saprophyticus*) and Gram-negative (*E. coli, S. typhimurium*) pathogens. Multi-drug-resistant pathogens like *Pseudomonas aeruginosa* always pose a critical problem to patients. Ansari et al. [87] used fresh leaves of *Cymbopogan citratus* to synthesize aluminum oxide (Al_2O_3) NPs, which possessed strong antibacterial activity against *Pseudomonas aeruginosa.* As the next-generation antimicrobials, Al_2O_3 NPs can be a very promising weapon in confronting multi-drug-resistant pathogens. Matussin et al. [106] used plant as biomaterials to produce Tin oxide (SnO_2) NPs for the photocatalytic, antibacterial, and antioxidant functions. The authors concluded that not only the reaction time, PH, temperature, amount of plant extract could affect the size, shape, and morphology of final NPs produced, but also other factors, such as different parts of plants, or even the colors of the flowers may influence the NPs' properties [106].

The same as microorganisms biosynthesis, plant extract biosynthesis methods are rapid, straightforward, and eco-friendly that are able to produce biocompatible and non-toxic NPs with advanced features [107]. More importantly, unlike microorganisms biosynthesis usually took a few hours up to a few days; plant extract synthesis could generate NPs within minutes: Au NPs could be produced within 2 min [108], 3 min [109], and 5 min [107], or Ag NPs within 2 min [110], 45 min [109], and 2 h [107]. Even though extensive research on plant extract biosynthesis with many accomplishments, the exact mechanism of how plant extract synthesis and stabilization of NPs remain mostly unknown [93]. It is essential and beneficial to gain a comprehensive understanding of how biological NPs are produced to enable us to synthesize them more efficiently.

Waste material biosynthesis

Waste material, such as natural waste [90, 92], kitchen waste [91], and electronic waste [111], can be used to synthesize various NPs as raw materials for various industrial applications and also provide us alternative direction for waste management. Since the source is waste material, the raw material cost can be meager, but extra cleaning and sterilization steps of waste material are required. Although the source can vary among a wide range, the necessary synthesis steps are quite similar to other biosynthesis methods. Used waste grass [90], used corncob [91], or wasted sugar cane bagasse [92] could be used to synthesize Ag NPs with desired features. Despite the above-mentioned biological sources, researchers have tried out electronic waste like waste compact disks to generate NPs [111]. Waste material biosynthesis not only helps us utilize the waste material in a cost-effective way, but also minimize the usage of potentially harmful chemical agents. Future research should focus more on exploring different types of waste materials to synthesize NPs with essential features.

Besides the most commonly synthesized Ag and Au NPs, other types of NPs, such as HAp NPs [9], TiO_2 NPs [74], aluminum oxide (Al_2O_3) NPs [87], nickel oxide (NiO) NPs [89], silicon carbide (SiC) NPs [111], and others, can be produced through biosynthesis. In many cases, biological NPs exhibited more outstanding biocompatibility than physico-chemically synthesized NPs [93]. However, biosynthesis still needs to be improved in a few areas: precise control of shape and size, mass production, repeatability, and consistency. We

Table 3 Features of biosynthesis methods of functionalized NPs

Synthesis methods	Advantages	Disadvantages	Main processing parameters	Characteristics of particles				
				Size	Size distribution	Shape	Crystallinity degree	Phase purity
Bacterial-mediated biosynthesis	Low cost, eco-friendly, non-toxic, rapid synthesis, simple process	Small scale, limited control over size and consistency, low repeatability	PH value, temperature, reaction time, aeration, mixing ratio	Nano	Various, narrow size can be achieved	Diverse, mostly spherical shape	Various	High
Fungi-mediated biosynthesis	Low cost, eco-friendly, non-toxic, rapid synthesis, simple process, potential large-scale production	Limited control over size and consistency, low repeatability	PH value, temperature, reaction time, aeration, mixing ratio	Nano	Various, narrow size can be achieved	Diverse, mostly spherical shape	Various	High
Algae-mediated biosynthesis	Eco-friendly, non-toxic, rapid synthesis, simple process	Small scale, low repeatability, slightly higher cost and preparation time than other biosynthesis methods, difficult in controlling size and monodispersity	PH value, temperature, reaction time, aeration, mixing ratio	Various, mostly nano	Various, narrow size can be achieved	Diverse, mostly spherical shape	Various	High
Yeast-mediated biosynthesis	Low cost, eco-friendly, non-toxic, rapid synthesis, simple process, easy controlling parameters	Small scale, limited control over size and consistency, low repeatability	PH value, temperature, reaction time, aeration, mixing ratio	Nano	Various, narrow size can be achieved	Diverse, mostly spherical shape	Various	High
Plant extract-mediated biosynthesis	Eco-friendly, straightforward, stable, cost-effective, potential large-scale production, fast (can be faster than other biosynthesis methods)	Limited control over size and consistency, low repeatability	PH value, temperature, reaction time, type of bio source, aeration, mixing ratio	Nano	Various, narrow size can be achieved	Diverse	Various	Various
Waste material-mediated biosynthesis	Extremely low raw material cost, eco-friendly, mostly non-toxic, rapid synthesis, simple process, waste management	Small scale, limited control over size and consistency, low repeatability, extra cleaning, and sterilization step of waste material	PH value, temperature, reaction time, source type, pressure, aeration	Nano	Various	Diverse	Various	Various

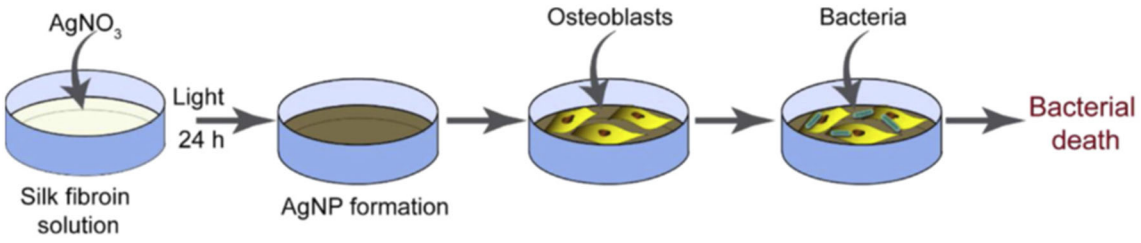

Fig. 5 A schematic process of in situ Ag NPs synthesis with antibacterial ability tested together MG-63 osteoblast seeded directly on films. Copyright Elsevier and reproduced under modification with permission [85]

are still at an early stage of developing NPs through biosynthesis. The features of commonly used biosynthesis methods of NPs are shown in Table 3.

Combination synthesis methods of NPs

Combination synthesis methods are recently developed. In general, combination procedures often lead to new possibilities of producing NPs with superior properties. Among the diverse combinations, the following methods have been quite useful: hydrothermal–mechanochemical [112–114], hydrothermal–hydrolysis [115, 116], hydrothermal–emulsion [61, 117], sol–gel combustion synthesis method [118, 119], sol–emulsion–gel synthesis method [120, 121], and a series of microwave-assisted methods as mentioned above [122–125]. The features of commonly used combination synthesis methods of NPs fabrication are shown in Table 4.

Hydrothermal–mechanochemical synthesis method

Hydrothermal–mechanochemical synthesis method, also known as wet mechanochemical method, is a method that merges mechanochemical with hydrothermal synthesis method. The high temperature will accelerate the reaction rate of dissolution, diffusion, and adsorption [9]. Suchanek et al. [126] successfully employed crystalline carbonate- and sodium carbonate-substituted HAp powder through the hydrothermal–mechanochemical synthesis method to synthesize HAp NPs with superior quality for bone grafting purpose. Ebrahimi et al. [5] used a precisely controlled and modified wet mechanochemical synthesis method combined with a controlled solid-state synthesis method to make HAp and β tricalcium phosphate (β-TCP) NPs with optimized physicochemical properties. The final physicochemical properties of the HA and β-TCP NPs come with high crystallinity (~ 100%) and homogeneity, with a reduced particle agglomeration size (6 μm) and lower crystallite/particle size (58 nm) as compared with the control samples [5]. The high crystallinity could enhance bone-bonding ability and stability, while the higher specific surface area can lead to improved protein and cellular interactions [5]. The team analyzed various processing parameters during the milling stage (weight %, milling ball diameter, milling time, sieve), post-synthesis period (cooling rate/duration, post-treatment), and calcination stage (heating rate, temperature, time). This novel combined synthesis method could produce NPs with advanced physicochemical properties, which could help with bone regeneration and have more potentially utilization in future biomedical applications [5].

Hydrothermal–hydrolysis synthesis method

Hydrothermal–hydrolysis synthesis method is a two-stage process combining boiling of sludge under high pressure and high temperature followed by rapid decompression. The purpose of high pressure and temperature is to accelerate the kinetic energy of hydrolysis to speed up the process. According to Parthiban et al. [115], HAp with different compositions, such as the substitution of sodium, magnesium, and carbonate ions, would affect its biological activity, degradability, and solubility. The team implemented the hydrothermal–hydrolysis method to manufacture carbonated HAp NPs, which was a potential biomaterial for bone reconstruction due to its high osteoconduction and biodegradability.

Hydrothermal–emulsion synthesis method

Hydrothermal–emulsion synthesis method combines the exclusive features of both hydrothermal and emulsion to produce NPs with controlled size distribution and minimal aggregation [9]. Lin et al. [117] made use of hydrothermal–emulsion to prepare stoichiometric single-crystal HAp NPs with mono-dispersion and narrow size distribution. The homogeneity in size distribution and shape of HAp are due to the nanoreactors and the soft template of the surfactants, while the high crystallization of HAp is due to hydrothermal treatment [117]. The HAp NPs obtained could be manipulated as a raw material to build dense bioceramics with excellent mechanical strength or applied as additives to fortify mechanical properties [117]. Sun et al. [61] synthesized

Table 4 Features of combination synthesis methods of functionalized NPs

Synthesis methods	Advantages	Disadvantages	Main processing parameters	Characteristics of particles				
				Size	Size distribution	Shape	Crystallinity degree	Phase purity
Hydrothermal–mechanochemical synthesis method	Usually low cost, rapid synthesis, large scale, no need pressure, or external heating	Poor size control	Processing temperature and time; milling ball size, number, geometry, and momentum; weight ratio of ball and powder	Micron to nano	Various	Diverse	Usually high	Usually high
Hydrothermal–hydrolysis synthesis method	Economically feasible, relatively low cost	Require heat and water in a huge amount	Temperature, pressure, reaction duration	Micron to nano	Various	Diverse	Usually high	Usually high
Hydrothermal–emulsion synthesis method	Minimal aggregation, uniform morphology, narrow size distribution	Small scale, relatively high cost	Temperature, PH value, reaction duration	Micron to nano	Narrow	Usually needle, rod	Usually high	Usually high
Sol–gel combustion synthesis method	Fast, convenient and effective, low reaction temperature, energy saving, both soluble and insoluble precursors can be used, high surface area, optimum agglomeration	Final product properties depend highly on the fuel used (heat generated during combustion, flame temperature)	Fuel type, PH value, annealing temperature, viscosity of sol	Nano	Narrow	Diverse	High	High
Sol–emulsion–gel synthesis method	Particles with specific size ranges, controllable purity, high bioactivity, high surface area, able to produce particles with various structures	High cost, time-consuming	sol/solvent volume ratio, viscosity of sol, PH value, stirring time, synthesis temperature/time	Nano	Narrow	Diverse	Usually low	High
Ultrasonic synthesis method	Fast and straightforward method, controllable morphologies and size of NPs, can link with other synthesis methods	Laboratory-scale only, high equipment cost	Power of ultrasonic, temperature, retention time	Nano	Narrow	Diverse	High	High
MW-assisted synthesis method	Uniform morphology, rapid synthesis, narrow size distribution, high yield, few side products, high effective method, homogenous heating	Small scale, relatively high cost	Microwave power/time, plus individual processing parameters	Micron to nano	Narrow	Diverse	Usually high	Usually high

HAp NPs through hydrothermal–reverse–emulsion synthesis method, where the PH value affected the morphology and size of the final product. PH value needed to be higher than 8.0 in order to produce phase-pure HAp NPs with sphere-like structure, whereas short nanorod or long nanorod structures could be synthesized when PH = 8.0 or < 8.0, respectively [61].

Sol–gel combustion synthesis method

Sol–gel combustion synthesis method is a combination of sol–gel and combustion synthesis methods, also known as solution combustion synthesis method. It is getting more attention recently because it is a fast, effective, and convenient method with low reaction temperature [118]. As shown in Fig. 6, sol–gel combustion synthesis method is formed by three main steps basically: combustion mixture formation, gel formation (turn sol to gel), and gel combustion [127]. This synthesis method provides a high exothermic reaction and releases a massive amount of heat, which causes the phase formation of most compounds finished during the process [128]. Sol–gel combustion synthesis method owns the advantages from both features that enable it to produce NPs with precise control of the size, high homogeneity, and high crystallization [128]. Moreover, the product quality depends highly on the fuel type, PH value, and annealing temperature [129]. Here, the fuel means any organic compound that reacts with the oxidant to start the combustion process.

Anjaneyulu et al. [119] produced wollastonite ($CaSiO_3$) with sol–gel combustion synthesis method by taking raw eggshell powder as a source of calcium, TEOS as a silicate of source, and glycine as the fuel. TEOS was added slowly to the premixed eggshell solution and then added glycine solution with continuous stirring and PH level maintained at 1 [119]. The sol was constantly stirred until a thick gel was formed. Then, the gel was heated up in a muffle furnace followed by calcination to generate the final product [119]. NPs obtained fell in very narrow size distribution and came with high phase purity [119]. The team further made a bone scaffold with wollastonite NPs which possessed excellent biocompatibility and bioactivity, which set an outstanding example to turn biowaste to biomaterials [119]. Choudhary et al. [130] used this method to generate calcium magnesium silicate, also known as akermanite ($Ca_2MgSi_2O_7$). The same as Anjaneyulu's team, this team also used biowaste (eggshell as the calcium source) to produce biomaterials. Akermanite NPs produced came with homogeneity, high crystallization, high phase purity, and biocompatibility [130].

Sol–emulsion–gel synthesis method

Sol–emulsion–gel synthesis method combines the features from both sol–gel and emulsion synthesis methods. Where usually a sol (water medium) is prepared and emulsified in an organic solvent to form droplets, then the droplets are stabilized through suitable surfactant, and gelling agents are added into gelate sol droplets to gel particles, followed by calcination of the gel particles to form NPs [131]. Sol–emulsion–gel synthesis method can produce particles with high surface area, specific size ranges, controllable purity, and high bioactivity. More importantly, it is able to produce particles with various structures [120, 121].

Moon and Lee [120] created radial wrinkle structural mesoporous silica NPs with full control of the inter-wrinkle distance, which can be utilized as drug delivery with smart releasing times. Li et al. [121] produced radial mesoporous bioactive glass NPs (rMBGs) using this combined synthesis method (Fig. 7). Cetylpyridine bromide, cyclohexane, and isopropanol were dissolved in deionized water first, and later, TEOS was added to the solution for hydrolyzation, with $Ca(NO_3)_2$ added later as calcium precursor for the reaction. After the washing and freeze-dry steps, the final collected precipitate was calcined as post-treatment. The obtained rMBGs were formed with a stable internal mesoporous structure with radial fibers. The large pore volume, the sufficient surface area, and the radial structure (less agglomeration) made rMBGs excellent drug carriers. Other researchers also obtained mesoporous silica NPs or core–shell silica NPs through this method [132–135], and the unique properties made silica NPs perfect for drug delivery or nanoreactors for chemical transformations.

Ultrasonic synthesis method

Ultrasonic synthesis method, also known as sonochemical synthesis method, is one of the earliest techniques employed to prepare NPs. It is a fast and straightforward method that utilizes ultrasound to enhance chemical reactions of molecules to produce NPs. Ultrasonic cavitation will be formed when the liquids are under ultrasonic irradiation. These cavitations can cause a series of extreme physical and chemical effects for chemical reactions [23]. The extreme internal conditions such as high temperature (up to 5000 °C), high pressure (up to 1000 atm), and high cooling rate (up to 10^9 K/s) make this unique synthesis method come with its advantages: fast speed, simple process, and controllable morphologies of NPs produced [136]. Besides the power of ultrasonic, other parameters such as temperature and retention time will affect the particle size. In addition, ultrasonic synthesis method can produce NPs or act as an assistant to other synthesis methods if needed [137].

Xu et al. [138] used an ultrasonic-assisted aqueous precipitation synthesis method to produce single-phase nanocrystallized calcium silicophosphate (CPS) NPs. The team produced CPS NPs with and without ultrasound, and the results showed that the cavitation effect caused by ultrasonic could improve

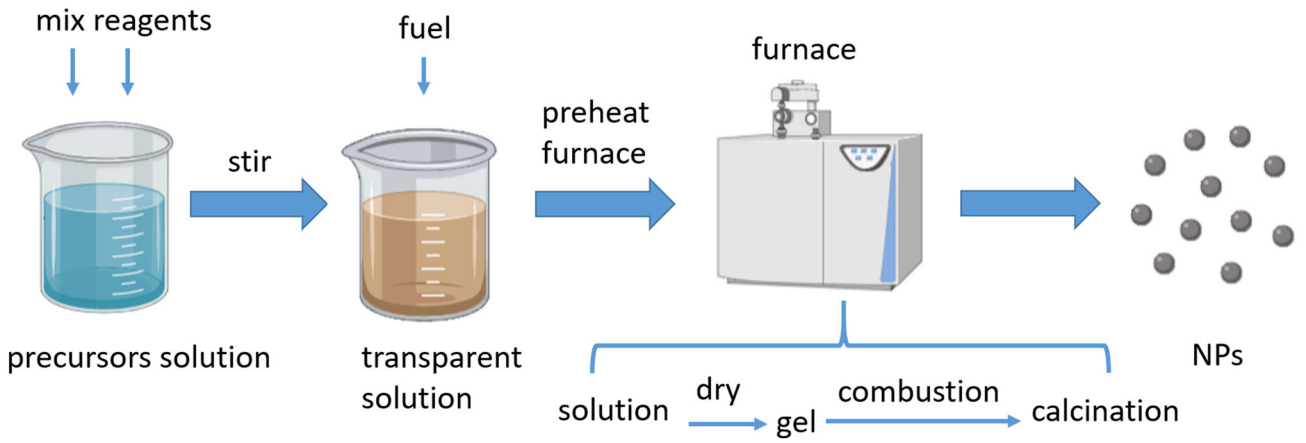

Fig. 6 A schematic process of a standard sol–gel combustion synthesis method

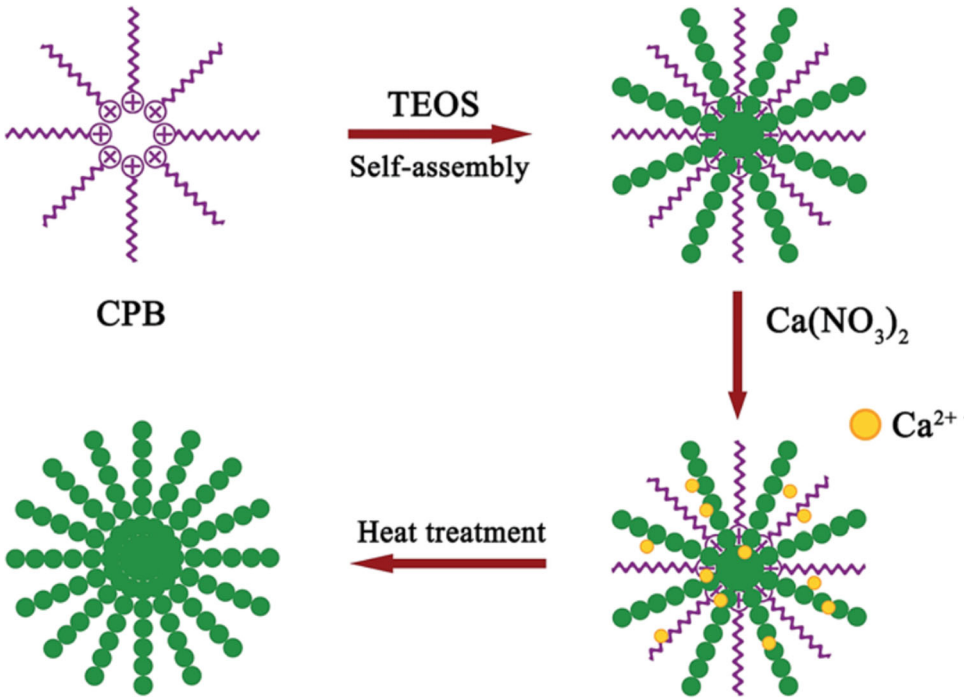

Fig. 7 A schematic illustration of sol–emulsion–gel synthesis method to produce rMBGs. Copyright Royal Society of Chemistry and reproduced with permission [121]

the speed and uniformity of chemical reaction [138]. Figure 8 shows how nanocrystallized CPS NPs are prepared with and without assistance from ultrasonic [138]. Calcium hydroxide ($Ca(OH)_2$), TEOS, and phosphoric acid (H_3PO_4) were mixed together as the starting reagents to synthesize precursors [138]. Then, the samples were divided into two groups: the ultrasonic-assisted aqueous precipitation group and the traditional aqueous precipitation group. With ultrasonic assistance, the calcination temperature of CPS NPs was reduced from 1350 °C to 1000 °C. Nanocrystallized CPS NPs fabricated from ultrasonic-assisted aqueous precipitation synthesis method that demonstrated better sinterability, bioactivities, and osteogenic activity [138]. CPS NPs demonstrated enhanced sinterability, bioactivities, and osteogenic activity, which proved to be a promising biomaterial for bone grafting.

Besides combined with precipitation synthesis method, ultrasonic can be linked with emulsion synthesis method as well. Alizadeh et al. [139] fabricated cadmium sulfide (CdS) NPs with controllable size and morphology through ultrasonic-assisted emulsion synthesis method. The team adjusted various manufacturing parameters to achieve the best quality. They found out that ultrasonic power and retention time could affect the size of the particles the most. With the ultrasonic added in, the whole process became relatively fast as compared to emulsion synthesis method [139].

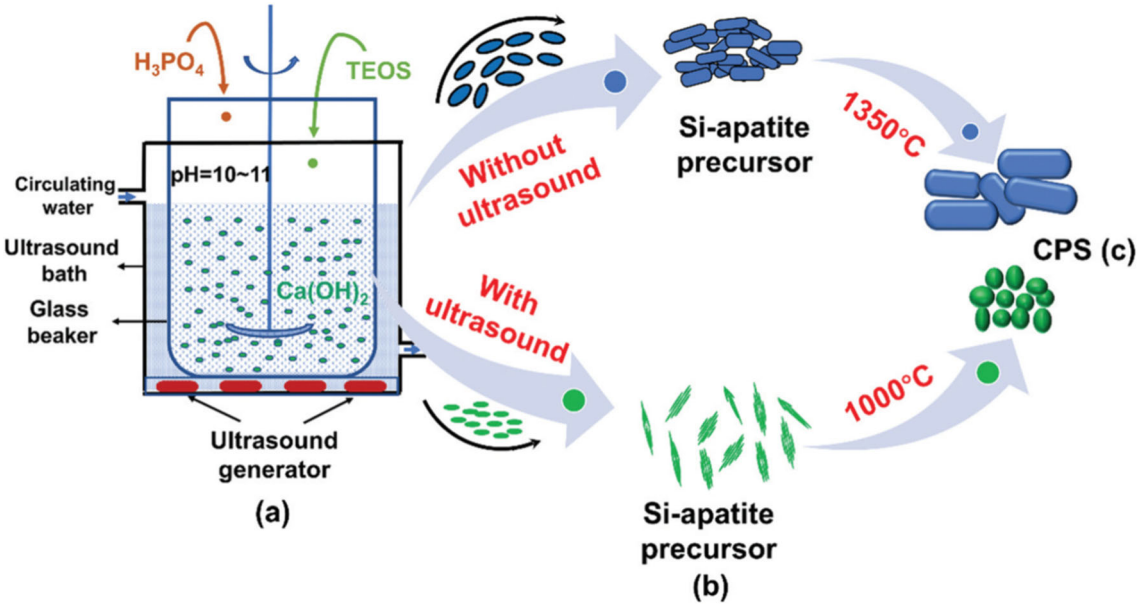

Fig. 8 Please change to: Fig.8 How nanocrystallized CPS NPs are prepared with and without the assistance from ultrasonic. (**a**) shows the experimental setup, with $Ca(OH)_2$, TEOS, and H_3PO_4 as starting agents; (**b**) shows the uniformity of chemical reaction and dispersity of Si-apatite precursor could be enhanced by ultrasonic; (**c**) shows the final CPS powders produced with ultrasound could reach greater specific surface area, better sinterability, and bioactivity. Copyright Royal Society of Chemistry and reproduced with permission [138]

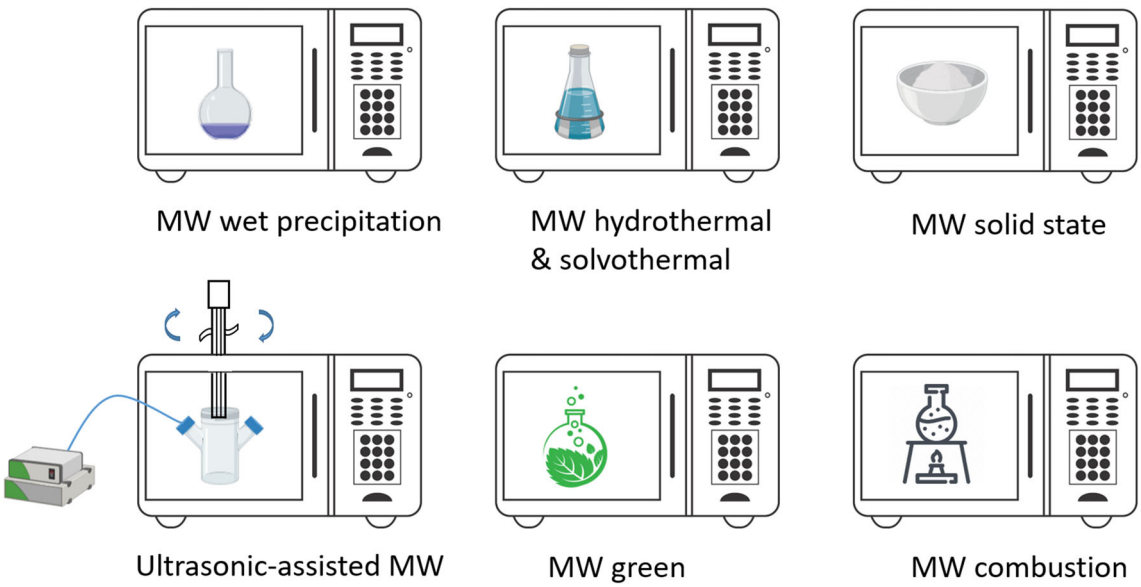

Fig. 9 A schematic process of a standard MW-assisted synthesis method

MW-assisted synthesis methods

MW-assisted synthesis methods apply microwave irradiation during the precipitation to expedite the process and generate NPs with better qualities [140–143]. MW-assisted synthesis methods can produce most types of NPs, including metallic NPs, inorganic NPs, polymeric NPs, and nanocomposites [144]. A basic understanding of MW-assisted synthesis methods and their interaction with materials is required to gain the advantages and limitations of MW-assisted synthesis methods [27]. MW-assisted synthesis methods are convenient and economical, thus expected to be optimized for mass production. A series of MW-assisted synthesis methods have been developed along the years: MW wet precipitation synthesis method [145, 146], MW hydrothermal and solvothermal synthesis method [122, 123], MW solid-state

synthesis method [147, 148], ultrasonic-assisted MW synthesis method [149, 150], MW green synthesis method [89, 151], and MW combustion synthesis method [125]. All these MW-assisted synthesis methods are fast and straightforward as compared to the methods without MW-assisted. These fine-tuned methods can produce NPs with high purity and ultrafine size in small scale. Figure 9 presents a summary of the commonly used MW-assisted synthesis methods.

HAp NPs were created with MW wet precipitation synthesis method that combined microwave irradiation and biomimetic approach with synthetic body fluid (SBF) used [146]. It was a fast, straightforward, homogenous, and efficient process to produce HAp NPs. The team creatively used calcium phosphate (CaP) in SBF as precursors to generate HAp NPs, while the precipitation process of bioactive CaP in normal SBF took a few days [146]. Therefore, the authors chosen concentrated SBF ($10 \times$ SBF) to expedite the process, and with lower phosphate contents to avoid forming giant crystal during precipitation [146]. The $10 \times$ SBF stock solution was prepared and separated into the first four groups with various microwave processing duration and power, the 5th group with conventional heating, and the 6th group with room temperature [146]. As a result, the configuration with microwave at 600 W and 9×30 s was determined to be the best for HAp NP production [146]. With processing parameters optimized, the team managed to produce HAp NPs with high purity and quantity, high biocompatibility, small particle size, and narrow size distribution [146].

Han et al. [123] synthesized HAp NPs with 10-30 nm diameter through MW hydrothermal synthesis method, and the overall high purity and ultrafine size of NPs were due to microwave assistance. Through a series of microwave irradiation, $Ca(OH)_2$ and H_3PO_4 solutions were heated up, reacted, and cooled down inside the vessel to form HAp NPs [123]. Various combinations of Ca/P ratio, microwave energy, and reaction time were tested to find out the optimal configuration: Ca/P ratio of 1.67, 550 W of microwave energy, and 4 min of reaction time [123].

MW solid-state synthesis method was used to produce zinc calcium phosphorous oxide (ZCAP) NPs [148]. The microwave furnace acted as a heating and irradiation device in the process. The authors concluded that ZCAP NPs generated from MW solid-state exhibited higher thermal stability, smaller sizes, and higher crystallinity than the conventional solid-state synthesis method [148]. MW solid-state synthesis method has been widely accepted due to its advantage: straightforward and fast irradiation process, uniform heating, less energy consumption, and increased diffusion process [148].

Liang et al. [149] used ultrasonic-assisted MW synthesis method (or named as sonochemistry-assisted MW synthesis method) to fabricate mesoporous HAp NPs in a fast and effective way based on the synergistic effect of microwave and ultrasound [149]. Microwave irradiation could add several advantages to the system, such as rapid heating, high reaction rate, and low power consumption, while ultrasonic could generate extremely high temperature, pressure, and cooling rate for the acoustic cavitation process [149]. During the synthesis process, microwave radiation also played an essential and dominant role in mesoporous generations, while ultrasound played a supporting role [149]. HAp NPs produced with microwave only or ultrasonic only were used as comparison groups as well. The images showed that HAp NPs generated with ultrasonic-assisted MW synthesis method came with the best crystal and mesoporous structure. In contrast, HAp NPs produced from ultrasonic only showed particle agglomeration [149]. Both these two methods can promote the reaction: Microwave can offer dielectric heating to act as a homogeneous heater for the growth of novel nanostructures, while ultrasound can release highly focused energy through shockwave to synthesize NPs quickly [150, 152]. A synergistic reaction can be triggered when these two methods are implemented together that can help the HAp NPs grow with high crystal and mesoporous structure [149].

Mani et al. [89] used MW green synthesis method (MW-assisted extracellular synthesis) to fabricate NiO NPs. Fresh leaves of *Plectranthus amboinicus* were cleaned, dried, and then mixed with distilled water. The mixed solution was boiled and then added into NiO solution [89]. The final solution was inside a microwave oven for processing, followed by centrifugation and dried up in a high-temperature environment [89]. The final dried NiO NPs collected exhibited enhanced physicochemical properties and better mineral deposition ability [89]. As discussed before, Al_2O_3 NPs could also be produced through MW-assisted extracellular synthesis [87].

MW combustion synthesis method was utilized by Gayathri et al. [124] to produce europium-doped paramagnetic gadolinium oxide ($Eu:Gd_2O_3$) NPs. Gadolinium nitrate ($Gd(NO_3)_3$), europium nitrate ($Eu(NO_3)_3$), and citric acid with water were mixed together and heated up in a hot plate to form a gel-like product and heated up the whole compounds in a microwave oven to run the combustion treatment to obtain porous $Eu:Gd_2O_3$ NPs [124]. $Eu:Gd_2O_3$ exhibited strong magnetic and luminescent properties, which could be used as a contrast agent in MRI and optical functions in cell imaging and guidance [124]. While $Eu:Gd_2O_3$ NPs were slightly toxic, therefore the author coated silica on them to increase their biocompatibility [124]. HAp NPs are always considered one of the most suitable candidates for bone substitutes. However, HAp NPs themselves do not possess antimicrobial abilities or drug-carrying abilities. Despite multiple existing HAp NP synthesis methods, such as sol–gel, solid-state, or hydrothermal, Lamkhao et al. [125] used this novel MW combustion synthesis method to produce HAp NPs with radicals. These HAp NPs with

radicals possessed strong antibacterial ability [125]. Radicals produced from microwave radiation were confirmed by the authors to be the leading cause of antibacterial ability [125]. Other researches also pointed out that the materials produced through microwaves also come with antibacterial ability [153]. The exact mechanism of how microwave radiation can produce radicals needs to be comprehensively studied to further its applications.

Challenges and future directions

NPs with unique features shall be utilized in order to overcome the current limitations. Functionalized NPs are expected to serve multiple functions within a single system; for example, drug-loaded SPION can be used in cell imaging while providing mechanical support to the scaffold and expediting the bone healing process. Therefore, advanced synthesis methods are needed to produce the next-generation NPs. One potential solution is to develop new synthesis methods. Any new synthesis methods must base on a full understanding of thermodynamic, kinetic, or natural processes of the synthesis. It should consider multiple aspects, including feasibility, cost, environmental impact, and quality of NPs, which is a challenging task. Besides the new synthesis methods, an alternative solution is through combining the current synthesis methods, such as use microwave or ultrasonic to assist the existing synthesis methods. Combination synthesis methods can produce new possibilities to improve the mechanical and biological properties of NPs. The third possible solution is improving the existing synthesis methods: utilizing better equipment, using more suitable chemical/solvent, implementing precise control over the entire process, and optimizing processing parameters.

Regardless of which solution we choose for the fabrication of NPs, there are three fundamental factors that should be considered in advance. Firstly, the most suitable NPs based on their individual properties shall be chosen for different applications, followed by designing NPs with specific structures and properties accordingly to fulfill the requirement. The composition, structure, surface chemistry, physical properties, and targeting ligands shall be carefully tailored in order to make them multi-tasking.

Naturally, how to equip these NPs with the predesign qualities in a consistent manner becomes the next question. There are so many aspects to consider for specific nanoparticle production, such as application requirements, processing parameters adjustment, and properties of NPs. Furthermore, even though there are various synthesis methods to produce NPs, almost all synthesis methods cannot meet the high standard requirements of the applications nowadays, which usually require NPs to be economically produced with a narrow size distribution, perfect morphology and shape, high crystallinity, and high phase purity consistently. Therefore, how to choose the most suitable synthesis method and implement it becomes very critical to the success of NP production.

Lastly, in order to choose the most suitable synthesis method, we need to fully understand all the underlying mechanism of each synthesis method, which we are still far away from it. For example, still many questions remain for biosynthesis, such as how does each processing parameter affect the properties of NPs produced? Or why NPs generated from biosynthesis show better biocompatibility than most other methods? Or are there any limitations of biological sources? Or how the shape and size of NPs can affect their functions and efficacies? All these unsolved questions may hinder our way to utilize every synthesis method fully.

In summary, this paper has generally reviewed the standard synthesis methods of NPs. In conclusion, NPs are associated with great benefits and potentials in numerous applications that overwhelm their shortcomings. Considerable research on improving synthesis methods is critical for us to utilize NPs further.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval This article does not contain any studies with human or animal subjects performed by any of the authors.

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