A comprehensive and systemic review of ginseng-based nanomaterials: Synthesis, targeted delivery, and biomedical applications

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A comprehensive and systemic review of ginseng-based nanomaterials: Synthesis, targeted delivery, and biomedical applications

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Abbreviations: APTEOS, 3-(aminopropyl)triethyloxysilane; APTMS, (3-aminopropyl) trimethoxysilane; AuNPs, Gold nanoparticles; BA, betulinicacid; BBB, blood–brain barrier; BG-AuNPs, black *P. ginseng* root gold nanoparticles; BSA, bovine serum albumin; CK, compound K; CK-NPs, CK loaded O-carboxymethyl chitosan nanoparticles; DHA, dihydroartemisinin; DMSO, dimethyl sulfoxide; DSPE-PEG, (1,2- distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethyleneglycol)-2000]; DSPE-PEG, (1,2- distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethyleneglycol)-2000]; DSS, disuccinimidyl suberate; FA-Rg5-BSA, folic acid modified BSA nanoparticles; FDA, US Food and Drug Administration; FoxO3a, Forkhead box O3 proteins; GC, glycol chitosan; GDNPs, extracellular vesicles (EVs)-liked ginseng-derived nanoparticles; GNP-CK-CopA3, microbial synthesized ginseng nanoparticles; GRAS, Generally Regarded as Safe; GS25, 25-OCH3-PPD ginsenoside; HA, hyaluronic acid; HAS, magnetic human serum albumin nanospheres; HCPT, hydroxycamptothecine; iNOS, nitric oxide synthase; LPS, lipopolysaccharide; LRP-1, low-density lipoprotein receptor-related protein-1; mPEG- PLGA, poly(ethylene glycol)-poly(lactide-co-glycolide); MRI, magnetic resonance imaging; MSiNPs, mesoporous silica nanoparticles; MTX, methotrexate; NaBH4, sodium borohydride; NO, nitric oxide; PBS, phosphate buffer solution; PC, phosphatidylcholine; PLGA, poly (lactic-co-glycolic acid); PS, polysaccharides; PVA, polyvinyl alcohol; PVP, polyvinylpyrrolidone; P-gp, P-glycoprotein; Rb1/PPD NPs, Rb1/ protopanaxadiol; ROS, reactive oxygen species; (PEG)-PLGA, poly (ethylene glycol)-PLGA NPs.

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Abstract

Among 17 Panax species identified across the world, *Panax ginseng* (Korean ginseng), *Panax quinquefolius* (American ginseng), and *Panax notoginseng* (Chinese ginseng) are highly recognized for the presence of bioactive compound, ginsenosides and their pharmacological effects. *P. ginseng* is widely used for synthesis of different types of nanoparticles compared to *P. quinquefolius* and *P. notoginseng*. The use of nano-ginseng could increase the oral bioavailability, membrane permeability, and thus provide effective delivery of ginsenosides to the target sites through transport system. In this review, we explore the synthesis of ginseng nanoparticles using plant extracts from various organs, microbes, and polymers, as well as their biomedical applications. Furthermore, we highlight transporters involved in transport of ginsenoside nanoparticles to the target sites. Size, zeta potential, temperature, and pH are also discussed as the critical parameters affecting the quality of ginseng nanoparticles synthesis.

KEYWORDS
biomedical applications, ginseng nanoparticle synthesis, ginsenoside based nanoparticles, green synthesis, microbial synthesis, Panax species, polymer-based ginsenoside nanocarrier, targeted delivery

1 | INTRODUCTION

Panax species, commonly known as ginseng are the most popular medicinal plants belong to the family *Araliaceae*. Given the long history of using *Panax ginseng* and *Panax quinquefolius* in traditional Chinese medicine that dates back to about 5000 years ago, several beneficial properties of these medicinal plants are supported by extensive clinical studies over the past few years.[1] Ginseng is slow growing plant that requires 6 years to attain maturity.[2] So far 17 different *Panax* species such as *Panax trifolius*, *Panax bipinnotifidus*, *Panax elegantior*, *P. ginseng*, *Panax japonicus*, *Panax major*, *Panax notoginseng*, *Panax omeiensis*, *Panax pseudoginseng*, *P. quineuefolius*, *Panax sikkimensis*, *Panax sinensis*, *Panax stipuleanatus*, *Panax vietnamensis*, *Panax wangianus*, *Panax zingiberenensis*, and *Panax sinensis* have been reported and grown in more than 10 countries (Figure 1), distributed and consumed in more than 35 countries across the world.[3,4]

The unique bioactive compound of ginseng is triterpenoid saponins called as ginsenosides. They exist in different isoforms in various parts of the plant and are species specific. They are widely used in the synthesis of various types of ginseng nanoparticles (Figure 2).

About 300 ginsenosides are identified and isolated from different Panax species.[11] Several ginsenosides are being identified from various Panax species that have pharmacological properties but poor bioavailability.[12,13] Despite promising biological activities of ginseng metabolites, poor absorption rate (<5%) in the gastro-intestinal tract resulted in the low bioavailability. It is possibly due to the interaction of ginsenosides with ion channels, cell

membranes, extracellular and intracellular receptors through alteration in the transcriptional level,[14,15] limited solubility as well as cytotoxicity to normal cells that holds their way to clinical trials.[16–18] The efflux transporters also pump ginsenosides out of the cells.[17,19–21] For instance, ABC efflux transporters and poor membrane permeability are the major reasons for the Rh2 poor absorption. To avoid this, drug delivery techniques and biomolecular conjugation of ginsenosides are proposed as the powerful strategies to improve ginsenoside penetration across the biological membrane and enhance their bioavailability.[22] Nanotechnology is considered as one of the elite alternative modern technologies in all areas of science. Until recently, different kinds of phytochemicals and compounds from ginseng were used in the synthesis of nanoparticles and tested for their biomedical applications including anticancer, antiobesity, anti-inflammatory, antimicrobial, and biosensors. Among various Panax species, three species *P. notoginseng* (Chinese ginseng), *P. quinquefolius* (American ginseng), *and P. ginseng* (Korean ginseng) are mostly used for nanoparticle synthesis.[23] Therefore, our review focusses further on the nanoparticle produced from these highly valued Panax species.

Various methods such as green synthesis, microbial synthesis, lipid based, inorganic and polymeric nanoparticles are used for ginseng nanoparticle synthesis (Figure 3, Box 1).

Each type of synthetic methods has their own advantages and disadvantages. Green synthesis is found to be safe, simple, one-pot, cost-effective, environmentally friendly, producing biocompatible nanoparticles, and applicable in various biomedical and pharmacological applications.[30–35] Furthermore, plant system has been considered more advantageous over microbial system due to rapid synthesis of nanoparticles in shorter time. On the other hand, microbial synthesis requires complex steps and downstream processing procedures.[36,37] Nevertheless, microbial based nanoparticle synthesis has also advantageous because it offers rapid, cost-effective, harmless, and eco-friendly method that does not require

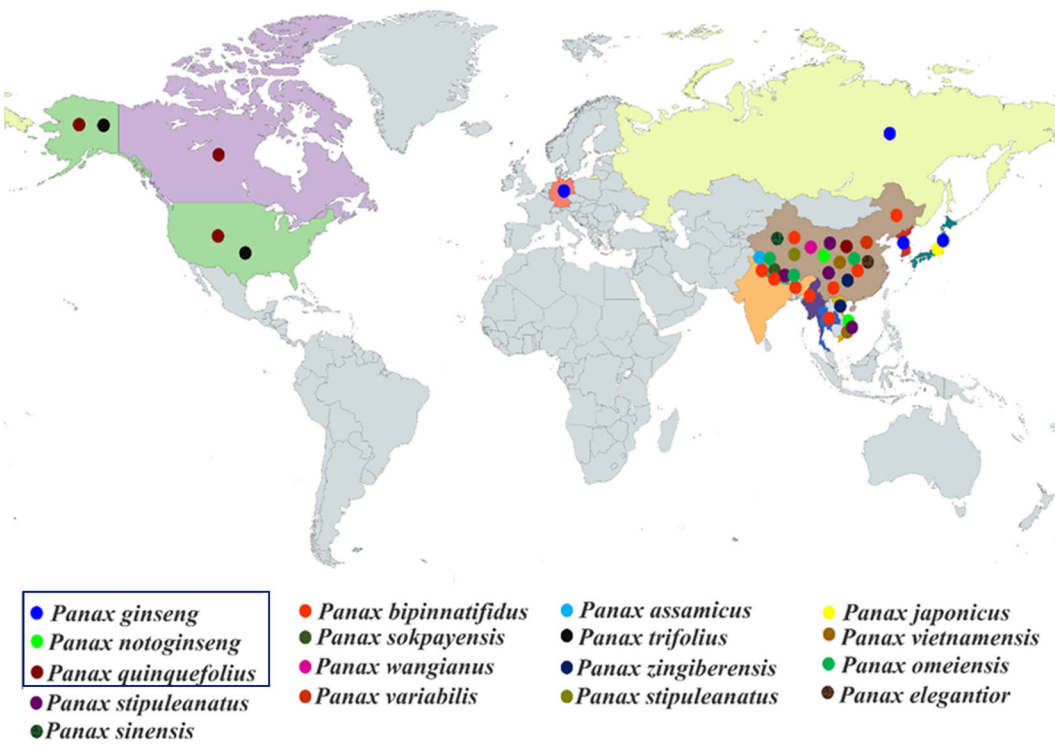

FIGURE 1 Reported Panax species used in ginseng nanoparticles synthesis. Distribution of different species of Panax across the world (https://powo.science.kew.org/).[3] Among these, *Panax ginseng*, *Panax notoginseng*, and *Panax quinquefolius* marked with box are widely used for ginseng nanoparticle synthesis. [Color figure can be viewed at wileyonlinelibrary.com]

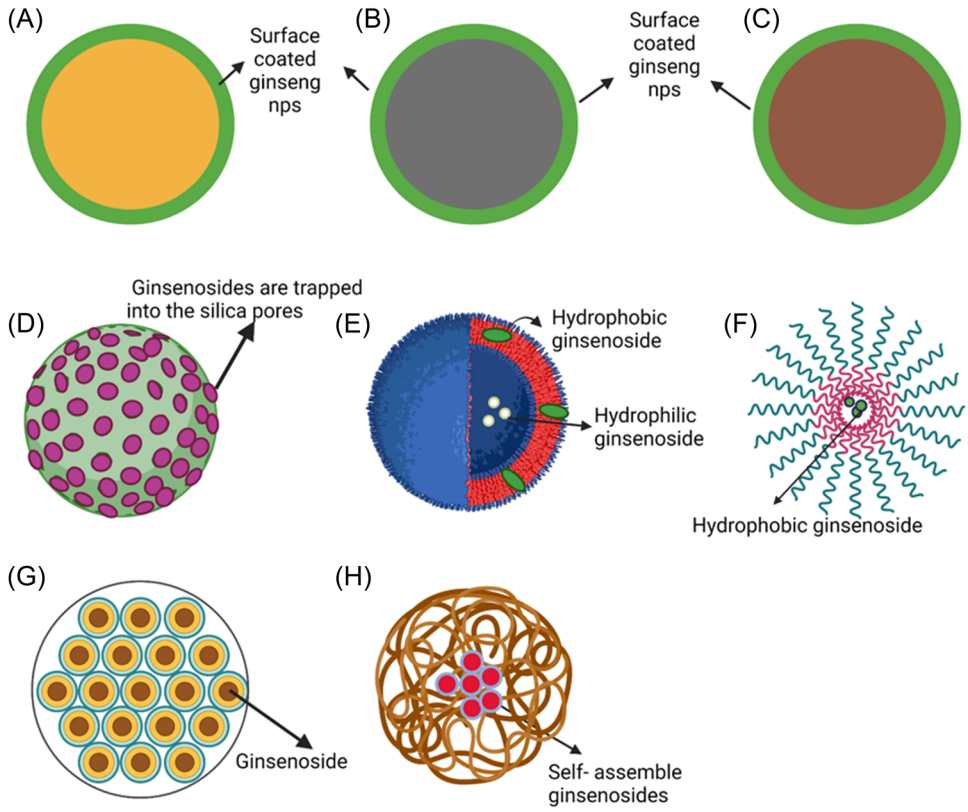

FIGURE 2 Representative nanostructures used to deliver ginseng biomaterials. (A) Gold,[5] (B) silver,[5] (C) zinc,[6] (D) mesoporous silica,[7] (E) liposome based,[8] (F) polymer based,[9] and (G) microfluid based nanoparticles,[10] (H) nano-formulation.[29] This figure was created using biorender software https://biorender.com/. [Color figure can be viewed at wileyonlinelibrary.com]

much energy for the synthesis of metal nanoparticles with broad diversity of sizes, shapes, composition, and physicochemical properties.[38] For the efficient drug delivery, polymers can be used broadly in wide range of applications in the field of biomedicine. However, use of synthetic polymers such as nylon, polyethylene, and polyester have several disadvantages including poor biocompatibility, lack of processing ability, poor drug loading ability, increased instability, and enhanced fragility. Therefore, the synthesis of biopolymers such as chitosan and biodegradable poly (lactic-co-glycolic acid) has gained promising role in drug delivery system due to their controlled delivery system, good biocompatibility, stability, nontoxic and nonimmunogenic, and enhanced therapeutic effects.[39] Microfluidics is also used to study the behavior of fluids at the microenvironments and therefore widely used in various field including biomedicine.[40] Compared to the polymer nanoparticles, microfluidic system possesses significant advantages including ease of fabrication, coherence, rapid, and cost effectiveness for synthesis of ginseng polysaccharide nanomaterials.[41] Furthermore, green approach of self-assembly such as Rb1 into ultra-micelles also showed promising therapeutic tool.[42]

In the past decade, only few reviews are reported at systemic and local delivery of ginsenoside using specific polymeric nanoparticles and nanofibers, increasing bioavailability considering administration route, delivering behavior, biocompatibility, and biodegradability of ginseng nanoparticles. Furthermore, a short review emphasized on various types of ginseng nanoparticles and application toward specific cancer treatment.[24,43,44] This review provides a systemic and comprehensive overview on the standard methods for synthesis of ginseng nanoparticles. To provide a quick glance on synthesis methods, we have also explained detailed process of various methods for synthesis of ginseng nanoparticle. This review highlights the role of different transporters involved in ginsenosides

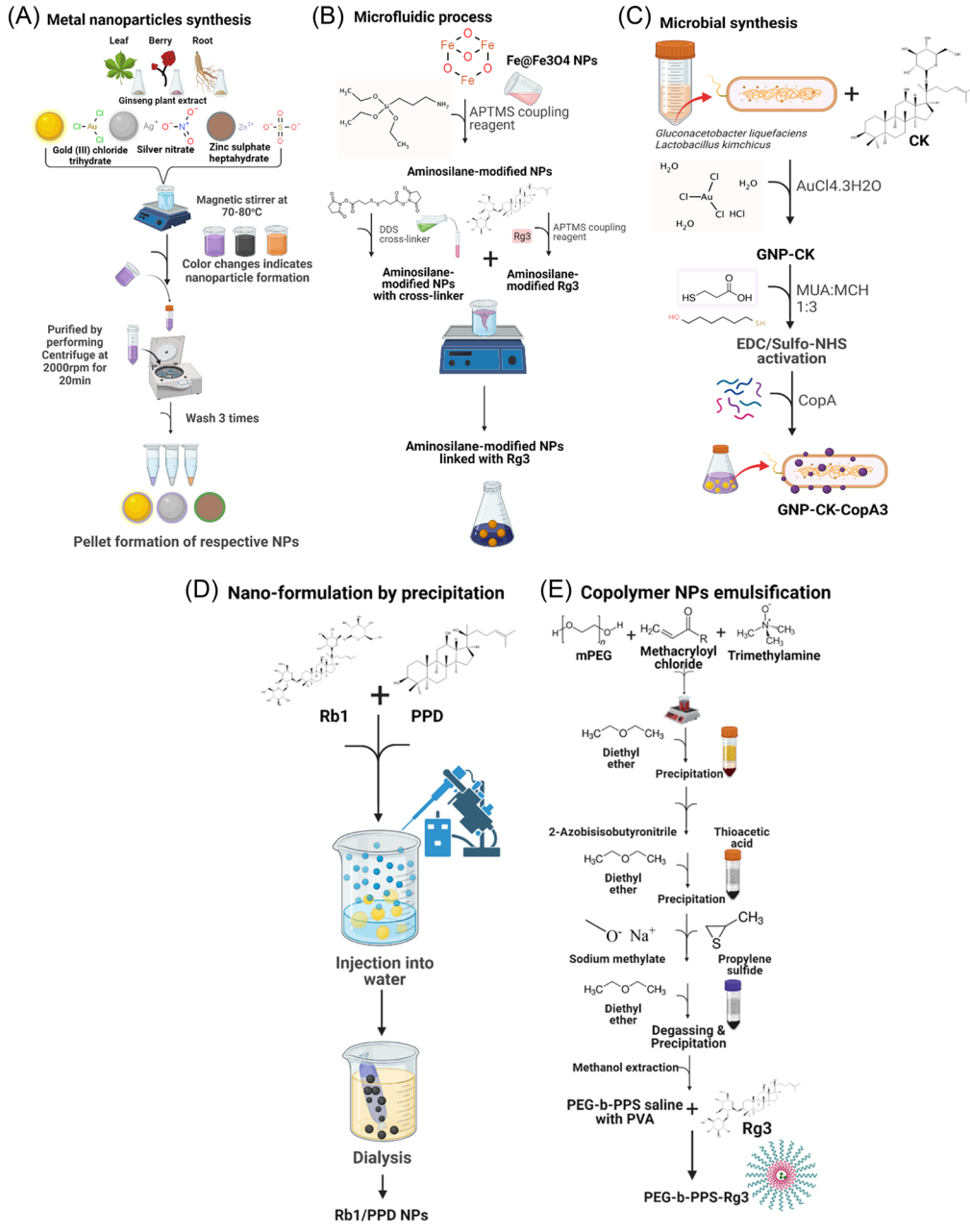

FIGURE 3 Schematic representation of different types of ginseng nanoparticle synthesis. (A) Metals such as gold, silver, and zinc are widely used to synthesis metal nanoparticles using various ginseng extracts including leaf, root, and berry from different Panax species.[24,25] (B) Fe@Fe3O4 nanoparticles synthesis through the microfluidic process.[10,26] (C) Microbial synthesis of gold nanoparticles using ginsenoside compound K, gold (III) chloride trihydrate, and probiotic bacterial strains.[27,28] (D) Ginsenoside Rb1/protopanaxadiol (PPD) nanoparticles (Rb1/PPD NPs) fabrication using precipitation method.[29] (E) Self-assembly of diblock copolymers of PPS and PEG for Rg3 encapsulation and delivery.[9] APTMS, (3-aminopropyl) trimethoxysilane; CK, compound K; DSS, disuccinimidyl suberate; EDC, 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide hydrochloride; GNP, gold nanoparticles; MCH, 6-mercapto-1hexanol; MUA, mercaptoundecanoic acid; PVA, polyvinyl alcohol; Sulfo-NHS, N-hydroxysulfosuccinimide. This figure was created using biorender software https://biorender.com/. [Color figure can be viewed at wileyonlinelibrary.com]

BOX 1 Experimental and mechanistic steps for producing ginseng nanoparticles from plants, iron oxide ginsenoside nanoparticles, microorganisms, and polymeric ginsenoside nanoparticles

Metal nanoparticle synthesis-using ginseng extract

For green synthesis, ginseng leaf, berry or root extracts were washed thoroughly, and boiled with relevant solvents or using aqueous solution. Depending on the type of metal nanoparticle synthesis, extract was mixed with (gold III) chloride trihydrate, silver nitrate or zinc sulfate heptahydrate and kept in magnetic stirrer at 70–80°C. The formation of nanoparticles with respect to metals were monitored by the color change in the medium. Later, the filtrates were purified by centrifugation and washed three times. Finally, the nanoparticles formed were collected in the form of pellet (Figure 3A).

Fe@Fe3O4 nanoparticle synthesis-microfluidic process

Polyvinylpyrrolidone and $FeCl_2{\cdot}4H_2O$ are dissolved into water to form the metal salt solution. Sodium borohydride into 1-Methyl-2-pyrrolidinone forms the reducing solution. The metal salt and reducing solution mixed in microchannel for nucleation and growth of nanoparticles at 60–90°C under inert atmosphere (nitrogen) protection. For the surface modification and to obtain aminosilane-modified nanoparticles, the nanoparticles are dispersed into the toluene solution that contains (3-aminopropyl) trimethoxysilane (APTMS), stirred, and precipitated. To activate amino groups on the surface of nanoparticles, nanoparticles mixed with the amine-active cross-linker of disuccinimidyl suberate (DSS) solution, centrifuged, dried, dissolved in phosphate buffer solution (PBS), centrifuged, and dried. The ginsenoside is added to an anhydrous toluene solution that contains APTMS, stirred, and precipitated. The aminosilane-activated ginsenoside mixed with the DSS activated nanoparticles, centrifuged, dried, and dissolved in PBS (Figure 3B).

Nanoparticle synthesis-microbial synthesis

The probiotic bacteria such as, *Gluconacetobacter liquefaciens* kh-1 and *Lactobalillus kimchicus* $DCY51^T$ were cultured in bacterial growth medium for 24 h. The well grown bacterial biomass were washed twice with 10 mM PBS buffer solution and re-suspended with sterilized dH_2O, gold salt (gold III chloride trihydrate) and dose-dependent concentration of compound K/ginsenosides. The sample mixture along with bacterial strains were incubated at 37°C with shaker for 24 h. The color (dark purple) changes were observed visually in culturing tubes denoted gold nanoparticle synthesis. The culture mixture was centrifuged at 2500*g* to remove supernatant has excess unloaded drugs and cultured medium. Further, drug-loaded trapped bacterial strains were sonicated and centrifuged again at 2500*g*. Lastly, the bacterial strains loaded with nanoparticles were centrifuged further with high-speed centrifugation at 28,000*g* and washed the pellet with dH_2O (Figure 3C).

Nano-formulations-precipitation

A precipitation method to prepare Rb1 NPs and PPD-loaded nanoparticles includes PPD and Rb1 dissolved in dimethyl sulfoxide, is followed by injection into water, stirring for 10 min, and dialysis in normal saline (Figure 3D).

Copolymer nanoparticles-emulsification

The critical parameters to be considered for synthesizing ginseng nanoparticle are provided in Table 1. Methoxy polyethylene glycol (mPEG), methacryloyl chloride, and trimethylamine are added to dichloromethane, stirring for 24 h, precipitation using cold diethyl ether. The precipitate, 2,

2-azobisisobutyronitrile, and thioacetic acid are mixed and dissolved in tetrahydrofuran (THF), cooled, degassed, stirred at 60°C for 24 h, and precipitated using cold diethyl ether. Precipitate and sodium methylate dissolved in THF with stirring for 30 min at 25°C. Then, poly propylene sulfide (PPS) is added to the mixture, and the solution was maintained at 60°C overnight with constant stirring. The solvent was removed, and the viscous liquid was extracted twice with methanol. Rg3 is dissolved into saline/ethanol and PEG-b-PPS in chloroform. The solution is emulsified by sonication for 3 min, followed by slow addition of saline with polyvinyl alcohol, and emulsification by sonication for 60 s. Solvents of ethanol and chloroform are removed from the final emulsion at 40°C (Figure 3E).

The different types of nanoparticles synthesis and critical parameters were summarized (Figure 3 & Table 1).

TABLE 1 Critical parameters to be considered during ginseng nanoparticle synthesis.

S. No.	Ginseng nanoparticles	Critical parameters
1.	Metal nanoparticle synthesis- using ginseng extracts	pH, time, temperature, metal concentration, surface charge and so forth.
2.	Fe@Fe3O4 nanoparticle synthesis-microfluidic process	Thermodynamic and kinetic parameters of Fe@Fe3O4 need to be precisely controlled by microfluidic strategy.
3.	Nanoparticle synthesis-microbial Synthesis	Bacterial growth condition, culture medium, pH of growth medium before and after addition of metal ion, type and concentration of plant extracts or secondary metabolites, toxic nature of metals and so forth.
4.	Nano-formulations-precipitation	For self-assembly of nano-formulations, choosing same backbone structure ginsenosides and optimizing composition of selected ginsenosides are crucial for self-assembly of hydrophobic structures and controlling particle size.
5.	Copolymer nanoparticles-emulsification	Selection of hydrophobic and hydrophilic polymers is crucial for efficient synthesis of amphiphilic block copolymer encapsulated ginsenoside.

transport across blood brain barrier to increase bioavailability. It also addresses biomedical applications of different types of reported ginseng and ginsenoside nanoparticles. We further emphasis on critical parameters, challenges, and prospects for synthesizing ginseng and ginsenosides based nanoparticles.

2 | SYNTHESIS OF GINSENG METAL NANOPARTICLES

2.1 | Gold nanoparticles (AuNPs)

Gold nanoparticles are widely studied metal nanoparticles in the field of medicine to deliver the drugs to the target sites. The temperature and time dependent extracellular multifunctional gold nanoparticles were

synthesized using aqueous extract of black *P. ginseng* root (BG-AuNPs) (Figure 3A). The phytochemicals present in the extract act as a reducing and stabilizing agent for the synthesis of purple color nanoparticles.[45] An unprecedented one-step green synthesis of AuNPs were synthesized in 10 min using red ginseng root extract without any additional special reducing/capping agents.[46] The gold nanoparticles were synthesized within 1 h using the root extract of Korean red ginseng. The presence of phytochemicals and ginsenosides in the root aided in reducing and stabilizing the nanoparticle synthesis.[47] *P. ginseng* leaves was also used in synthesis of spherical shaped AuNPs within 3 min.[25] The nanoparticle formation is due to the reduction of Au^{3+} to Au^{0} causing the solution to turn dark purple in 3 min at 80°C.[48] Synthesis of AuNPs using berry extract was also obtained without using hazardous solvents and capping agents.[49] Beside AuNPs, utility of red ginseng was also reported as an efficient and environmentally friendly reducing agent in reduction of graphene oxide (GO) as compared with the reduction by hydrazine.[50]

The single ginsenoside Rg3 was conjugated to spherical AuNPs using bifunctional linker of heptaethylene glycol. Hydroxyl group of Rg3 was bound with carboxylic acid end in heptaethylene glycol through the ester bond while the sulfhydryl group in heptaethylene glycol was bound with the gold nanoparticles.[51] The single ginsenosides of compound K (CK) and Rh2 were also utilized by one-pot green chemistry in the oil bath at 80°C to accommodate a synergistic chemical reduction of gold salts.[52]

2.2 | Silver nanoparticles (AgNPs)

A simple, rapid, inexpensive, and eco-friendly ultra-sonication-assisted silver nanoparticles have been successfully synthesized from roots of *P. ginseng*. It showed consistent dispersal of nanoparticles in liquid medium, and it was effective in breaking aggregates and enhanced the reaction rates. Ultrasonication for 3 h after addition of silver nitrate to the aqueous ginseng root extract resulted in conversion of solution color from colorless to dark yellow indicating the nanoparticle formation.[53] The green and rapid synthesis of monodispersed silver nanoparticles (BG-AgNPs) synthesized using black ginseng root extract exhibited temperature and time dependent changes. Increase in temperature (80–90°C) showed major absorption peaks at 412 nm indicating that 90°C is the optimum temperature for BG-AgNPs synthesis.[45] The one-pot, simple, and rapid green synthesis of highly stable and colloidal AgNPs has been performed using *P. ginseng* root extract as a reducing and capping agent by taking different parameters under consideration including time, concentration of precursor, concentration of both reducing and capping agent, and pH.[33] A facile, monodispersed, and stable AgNPs were synthesized using leaves of *P. ginseng*. The presence of phenolic acids, flavonoids, ginsenosides, and polysaccharides influenced the formation of brown color after 45 min of incubation at 80°C, indicating the formation of AgNPs.[48] Polysaccharides and phenolic compounds present in the *P. ginseng* berry extract were suggested to be involved in stabilization and functionalization of nanoparticles using green synthesis method.[49]

2.3 | Zinc nanoparticles (ZnNPs)

The utilization of plant extracts in the synthesis of zinc nanoparticles (ZnNPs) has gained much interest in the pharmaceutical and biomedical field because zinc is used as the preservative in various products including foods, pigments, plastics, and glasswares.[54,55] The extract of red ginseng roots can reduce zinc heptahydrate to produce ZnNPs. The heating temperature at 70°C is optimal to increase activation energy and reduce organic molecules for ZnNPs synthesis.[6]

2.4 | Silica nanoparticles (SiNPs)

Interesting structural properties of mesoporous silica nanoparticles (MSiNPs) for drug delivery include stability, large surface area, narrow particle size distribution, and surface silanol groups (Si–OH) for binding with drugs.[56] However, trapping drugs into the inner wall of the nanosized pores in MSiNPs protects the drugs from enzymatic degradation and premature release.[57] CK and Rh2 were loaded in 200 nm MSiNPs (4-nm pore size) with amide bond to enhance their efficacy. Under acidic condition, the amide bond could be hydrolyzed and thereby releasing CK and Rh2. In this method, addition of 3-(aminopropyl)triethyloxysilane (APTEOS) results in activated free amine groups on the surface and pores.[7]

2.5 | Iron oxide nanoparticles (Fe@Fe3O4 NPs)

Fe@Fe3O4 NPs synthesis through the microfluidic process includes several steps. First, NP surfaces modified with -NH_2 groups using a silane coupling technique using (3-aminopropyl) trimethoxysilane (APTMS) as the coupling reagent, followed by activation by the bifunctional amine-active cross-linker (e.g., disuccinimidyl suberate, DSS). The activated NPs cross-linked with the pre-activated ginsenosides by APTMS formed the desired nanomedicine with an excellent coupling effect (Figure 3B).[10,26]

The direct conjugation of ginsenosides CK and Rg3 with superparamagnetic iron oxide nanoparticles (SPIONs) was also a simple, fast, low-cost, high yield, and eco-friendly method. The maximum percentage of ginsenosides attachment to the SPIONs was 5%.[58]

3 | MICROBIAL SYNTHESIS OF GINSENG NANOPARTICLES

The microorganisms can interact with inorganic materials through direct or indirect approaches by various biochemical reactions. Predominantly, some bacterial strains such as, *Lactobacillus* sp. and *Gluconacetobacter* sp. can detoxify the metal by-products through oxidation or reduction process and convert metal ions into nanoparticles. The hydrophobic and large-sized ginseng secondary metabolites such as, Rh2, compound CK, and other ginsenosides were transformed into gold or silver coated nanoparticles by using bacterial strains including *Lactobacillus kimchicus* DCY51^T and *liquefaciens* Kh-1 (Figure 3C).[27,28] However, only few bacterial strains were reported the synthesis of microbial mediated ginseng nanoparticles using silver and gold. Extensive research should be carried out in this area for exploiting the use of microbes for ginseng nanoparticles synthesis and investigating their biomedical applications.

This viable green synthesis approach could be considered as an alternative approach to evade environmental pollution by physical or chemical synthesis. Recently, most of the microbes are abundantly engaged with different metal ions for nanomaterials synthesis including, gold, silver, iron, copper, pallidum, and titanium.[59,60] However, due to the toxicity of inorganic metals, most of them were not considered yet for biological synthesis of nanoparticles. The silver metal ions are well-known for its antibacterial activity, however some of the bacteria such as, into silver nanoparticles through the biochemical modification by their defensive mechanism.[61] Thus, the defense mechanism for their survival toward interaction with metal ions facilitates conversion of metals into nanomaterials through various biochemical reactions, such as oxidation or reduction to detoxify the metal ions into phosphate, carbonate, and sulfide forms.[62]

3.1 | Extra- or intracellular mediated ginseng nanoparticle synthesis

Microbial synthesis of ginseng nanoparticles is mainly involved microbial extra- or intracellular mediated surface modification through various biomolecules including, protein, enzymes, carbohydrates, and sugars of microbial

population (Figure 4).[28,63] The successful microbial ginseng nanoparticle synthesis was obtained through one-pot synthesis method using lactic acid producing bacterial strains such as, *Lactobacillus* and *Gluconacetobacter* strains.[28,63]

The extracellular mediated nanoparticle synthesis of inorganic metals (gold or silver) is mostly performed on the bacterial cellular surface or membrane through various biological reduction process such as extracellular enzyme reductase, nitrate reductase or hydroquinone-mediated redox reaction.[59,64,65] Specifically, the extracellular synthesis of gold or silver nanoparticles is mediated through enzymatic reduction process that converts silver ions into nanosized silver materials. The exopolysaccharides on the cellular surface or cell membrane of *Lactobacillus kimchicus* DCY51^T contribute to a possible biochemical enzymatic process for the reduction of gold metal ions into CK coated gold nanoparticles.[27] However, smaller sized DCY51^T mediated ginseng gold nanoparticles are transported and internalized into the cells through the cytoplasmic membrane. Meanwhile, microbial synthesized nanoparticles (peptide CopA3 surface conjugated CK loaded gold NPs) were internalized by membrane bounded cell organelles such as endosomes or lysosomes in inflammatory murine RAW 246.7 cells.[28]

The intracellular mediated nanoparticle synthesis is influenced by electrostatic interaction of positively charged metal ions with negatively charged cellular surface of bacteria that promotes enzymatical surface modification and helps diffusion of nanoparticles through cell wall by various stepwise mechanisms including, trapping, reduction, capping, and stabilization.[66,67] The physicochemical properties of inorganic metal ions such as size and surface modification play crucial roles to interact with microbial environment for the nanoparticle synthesis through various biochemical reactions including, reduction, aggregation, electrostatic interaction, van der walls, and hydrophobic forces. The secondary metabolites of ginseng have poor permeability and low solubility due to large-sized hydrophobic characteristic resulting in decreased bioavailability and intestinal absorption.[22,68] Whereas microbial mediated synthesis of ginsenoside nanoparticles negotiated well with the cellular membrane. They are internalized into the cytoplasmic organelles that aids structural conversion due to gastric juice and digestive bacterial enzymes through reduction, aggregation, and electrostatic interaction.[69] Furthermore, the bacterial strains such as, *Lactobacillus* sp. and *Pseudomonas* sp. involve electrostatic interaction of metal ions and cell membrane with enzymatic surface modification that enables nucleation of nanoclusters and reduces the metal ions into nanomaterials diffused into the cells through the cell membrane.[65,70]

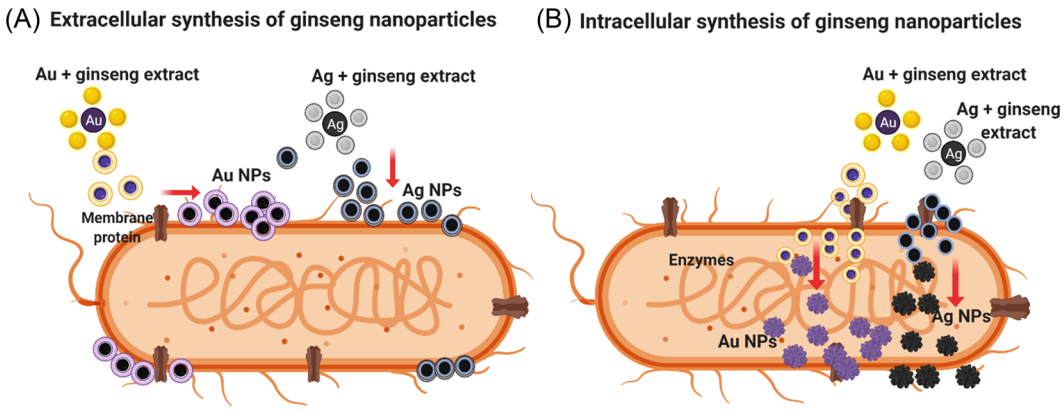

FIGURE 4 Microbial synthesis of ginseng nanoparticles. This figure was created using biorender software https://biorender.com/. [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Proposed microorganisms for microbial mediated ginsenoside nanoparticle synthesis

The nanoparticles such as magnesium oxide, silver, gold, copper oxide, and selenium synthesized by *Bacillus licheniformis*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus kimchicus*, and *Lactobacillus casei* showed significant biological activity including anticancer, antioxidant, and antimicrobial activities.[27,71–73] Although there are several studies investigated microbial mediated synthesis of nanoparticles in various biomedical field, studies about microbial mediated synthesis of ginseng nanoparticles are poorly investigated. Microbial synthesis using beneficial bacteria will offer several advantages including stable and efficient production of nanoparticles with enhanced biomedical applications. Microorganisms including *Bacillus* sp., *Lactobacillus* sp., *Pseudomonas* sp., *Alcaligenes* sp., and *Streptomyces* sp. are isolated from soil, food and other sources and listed as the putative microbes that can be used for microbial mediated ginseng nanoparticle synthesis. Therefore, phylogenetic tree was constructed for the suggested bacteria that can be used for ginseng nanoparticle synthesis (Figure 5). The 16S rRNA

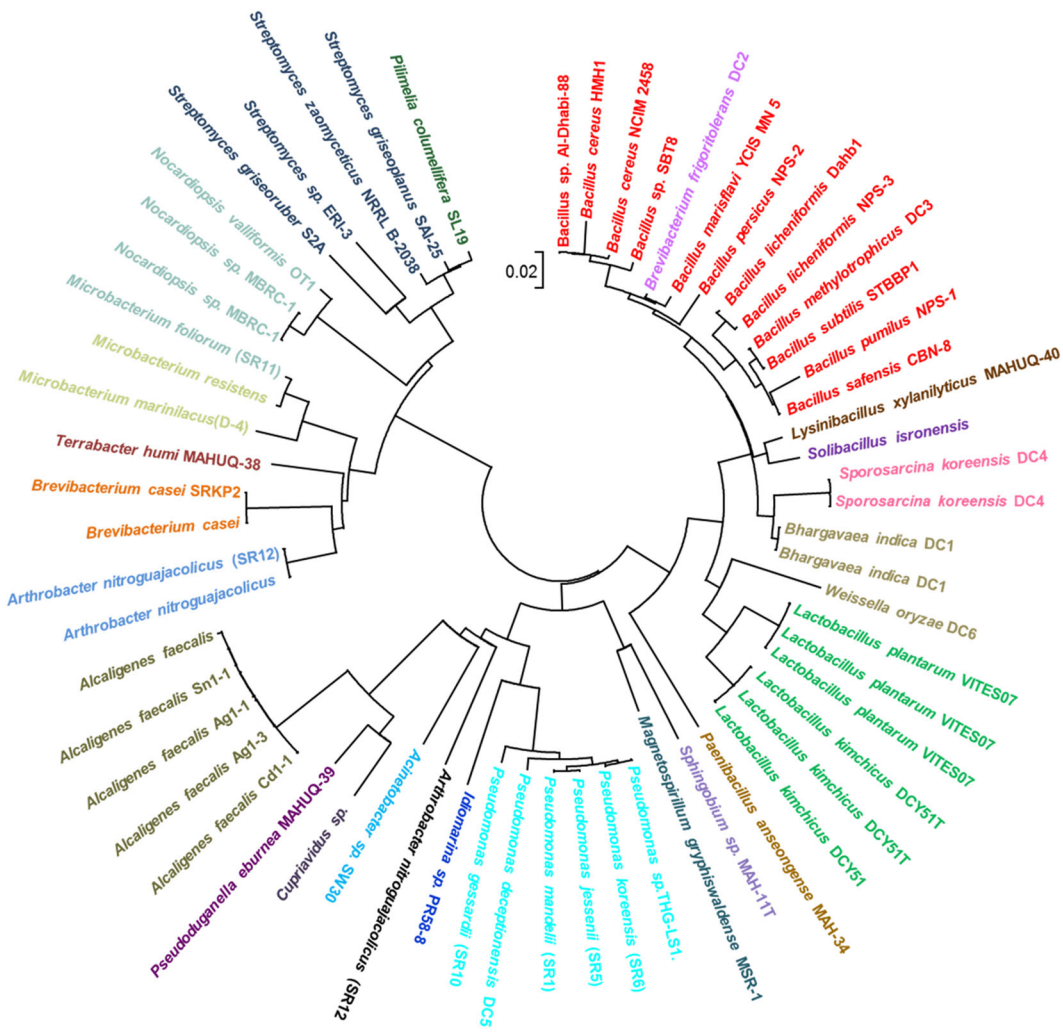

FIGURE 5 Phylogenetic tree constructed using neighbor-joining method based on 16S rRNA gene sequence analysis showing the phylogenetic relationships among different nanoparticles producing microorganisms. Scale bar, 0.02 substitutions per nucleotide position. [Color figure can be viewed at wileyonlinelibrary.com]

gene sequences of suggested bacteria were obtained from the GenBank database (http://blast.ncbi.nlm.nih.gov/Blast.cgi). The multiple sequence alignments were performed by using the CLUSTAL_X program[74] and the phylogenetic tree were constructed based on 16S rRNA gene sequences using the neighbor-joining method[75] in the MEGA 7.0 program,[76] with bootstrap values based on 1000 replications.

4 | SYNTHESIS OF GINSENG NANO-FORMULATIONS

Ginseng derived nanoparticles in the form of nanoemulsion were synthesized using *P. ginseng* root extract that enhanced the efficacy and kinetics by improving their oral bioavailability.[77] The amphiphilic molecules spontaneously self-assembled in an aqueous environment is the core-shell structure nanoparticle that is used for drug delivery system. Ginsenoside Rb1/protopanaxadiol (PPD) nanoparticles (Rb1/PPD NPs) called as "nano-ginseng" were fabricated using precipitation method that is a scalable, simple, and green economy process (Figure 3D). In this case, two PPD type ginsenosides of PPD and Rb1 self-assemble and form the inner hydrophobic core structure, while the sugar residues of Rb1 form the outer shell to enhance the dispersibility and stability.[29]

5 | SYNTHESIS OF POLYMER-BASED GINSENG NANOPARTICLES

To enhance the drug efficacy and improve the bioavailability, the biodegradable polymers are extensively used. Encapsulation of drugs with polymeric nanoparticles increases solubility, controls drug release, avoids effect of β-glycoproteins, improves drug targeting, and often resulting in improved efficacy while protecting the drugs from premature degradation.

5.1 | Poly (lactic-co-glycolic acid) (PLGA)

US Food and Drug Administration (FDA) approved poly (lactic-co-glycolic acid) (PLGA) for pharmaceutical applications. Rg3-loaded PLGA nanoparticles were prepared by oil-water emulsion and solvent evaporation technique.[18,78] Considering the acidic nature of PLGA monomers, 25-OCH3-PPD ginsenoside (GS25) was encapsulated into poly (ethylene glycol) (PEG)-PLGA nanoparticles using different methods including solvent emulsion-evaporation, emulsification-diffusion, and nanoprecipitation. However, GS25 was successfully encapsulated in PEG-PLGA by nanoprecipitation method with 89% encapsulation efficiency, more than 9% drug loading, and 43 nm particle size.[79]

5.2 | Serum albumin

Albumin, the most abundant plasma protein (more than half of the human plasma proteins), is stable over a wide range of pH (4–9) and it is also thermally stable while heating up to 10 h at 60°C without deleterious effects.[80] Considering the highest binding rate of albumin proteins and ginsenoside Rh2, albumin nanoparticles are recognized as the prominent nanocarrier produced using desolvation method.[81,82] Several albumin-based drugs and imaging agents are produced and available in the market, while some are undergoing clinical trials for various applications.[83] Ginsenoside CK and Rh2 entraped within bovine serum albumin (BSA) to form BSA–CK/Rh2 nanoparticles using desolvation method, that enhanced their aqueous solubility and stability.[82] Magnetic Fe_3O_4 nanoparticles are absorbed by tumor cells showing higher sensitivity to hyperthermia. While magnetic human serum albumin (HSA)

nanospheres loaded with 20(s)-Rg3 prepared by the desolvation-crosslinking technique could overcome the short half-life of Fe_3O_4.[84]

5.3 | Chitosan

Chitosan has received much attention due to several properties including nontoxicity, biocompatibility, biodegradability, low cost, and abundance.[85] However, due to poor solubility of chitosan, various chitosan derivatives are used extensively for the delivery of poor soluble drugs. The synthesis of ginsenoside CK loaded O-carboxymethyl chitosan nanoparticles (CK-NPs) enhanced solubility, stability, cytotoxicity, and cellular uptake of CK in prostate cancer cells.[86] Similarly, CK-NPs were prepared using amphipathic deoxycholic acid-O carboxymethyl chitosan carrier via combined self-assembly and sonication techniques. It improved the solubility of CK in water and promoted cellular uptake in vitro.[87] To enhance the stability and solubility of CK, an ionic cross-linking between Ca^{2+} ions of $CaCl_2$ and carboxyl groups of O-carboxymethyl chitosan was also used to entrap ginsenoside CK within O-carboxymethyl chitosan nanoparticles. The principal parameters affecting the formation of the nanoparticles are the concentration of polymer and cross-linker. In vitro drug release from the nanoparticles was pH dependent and the drug release rate was consistently higher at lower pH than that of higher pH.[86] This can be due to the protonation of amino groups that causes O-carboxymethyl chitosan swelling in an acidic environment.[88] Furthermore, the hydrophobic ginsenoside CK covalently conjugated to the backbone of hydrophilic glycol chitosan (GC) through the ester bond is hydrolyzed under acidic conditions to enhance the targeted delivery and water solubility. For that purpose, succinic anhydride treatment is needed to prepare CK-COOH, after which the amino group of GC was covalently coupled to CK-COOH in the presence of N-hydroxyl succinimide (NHS) and 1-ethyl-3- (3-dimethylaminopropyl)-carbodiimide·hydrochloride (EDC·HCl).[89]

5.4 | Poly (ethylene glycol) (PEG)

FDA approved PEG as the Generally Regarded as Safe. PEG with nontoxic, hydrophilic, nonionic, and low polydispersity index characteristics is a widely used drug carrier. The succinic anhydride can prepare active carboxyl-terminus of PEG to be used for conjugation with PPD aglycone ginsenoside (aPPD). Thus, the hydrophilic PEG was covalently conjugated to the hydrophobic aPPD through a pH-sensitive ester linkage. It triggers release in acidic conditions (endosomes, lysosomes, and tumor tissues) while reducing cytotoxicity to nontargeted regions.[90]

The micelles formed by amphiphilic block copolymers are also potential carriers for the delivery of hydrophobic drugs.[9] PEG with resistance to protein adsorption is usually used as the hydrophilic block. PPS with an extreme hydrophobicity is the hydrophobic block, oxidatively converted into a hydrophile in response to reactive oxygen species (ROS). Since a variety of injuries causes ROS accumulation, designing a ROS-responsive drug release system could improve the drug efficacy at the injury site. Thus, the ROS-responsive nanoparticles (PEG-b-PPS) was generated through the self-assembly of diblock copolymers of PPS and PEG for Rg3 encapsulation and delivery at the ROS-generating sites[9] (Figure 3E). Similarly, PEG-b-PPS homologous, pluronics F127 could also encapsulate Rg3 to enhance the antioxidant effects and solubility in heart injury model induced by doxorubicin (DOX).[91]

Moreover, the mPEG-b-P(Glu-co-Phe) copolymers were self-assembled in aqueous solution and then co-loaded with Rg3. Three components of the copolymer include, (1) PEG involved in nanoparticles protection from the enzymatic damage and prolonged circulation time, (2) glutamic acid units assist in the electrostatic interaction between the nanoparticles and Rg3, and thereby caused a pH sensitive drug delivery system within tumor tissues,

(3) phenylalanine units increase the aromatic/hydrophobic interactions within the inner core of the nanoparticles and cellular uptake of nanoparticles.[92]

5.5 | Hyaluronic acid (HA)

Amphiphilic HA derivative-based nanoparticles are fabricated for cancer therapy and diagnosis. Gelatin and HA nanoparticles were prepared and followed by addition of ginsenoside Rg3 in the electrostatic field preparation system.[93] Amphiphilic HA ceramide, lipids (1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy (polyethyleneglycol)-2000] [DSPE-PEG], and phosphatidylcholine [PC]) were used to develop a nanocomplex for Rg3 delivery. Lipids improved cellular permeability while the hyaluronic acid–ceramide (HACE)-based nanostructures are beneficial in self-assembly and targeting tumor via interaction of HA and CD44 cell surface receptor. Moreover, introducing PEGylated lipid (DSPE-PEG) could also form the hydrophilic PEG shell on the outer surface of nanocomplex. Rg3 with hydrophobic structure was encapsulated into the hydrophobic cavity in the nanocomplexes using a solvent evaporation method.[94]

Ginsenoside-modified nanostructured lipid carrier loaded with insoluble bioactive curcumin was also prepared by melt emulsification technique, in which water added to the melted lipids was homogenized to provide a uniform suspension.[95] Furthermore, the oral absorption of 25-OCH3-PPD with poor lipophilicity and hydrophilicity could be improved by nanoemulsion loaded with 25-OCH3-PPD-phospholipid complex that was prepared by solvent evaporation.[96]

6 | SYNTHESIS OF GINSENG-BASED MICELLES AND VESICLES

Plant derived extracellular vesicles are proven to have no toxicity to human and can be used to deliver chemoprotective agents and other biomaterials during cancer treatments.[97] A novel nanoparticle like extravesicular was isolated using *P. ginseng* root extract through density gradient centrifugation using ultrasonification method.[98]

Micelles could be formed by ginsenoside Rb1 in aqueous solutions. Self-assembled Rb1 micelles with ultra-small particle size (<8 nm) were utilized for the ocular diclofenac delivery system. The encapsulation of drug within Rb1 micelles using thin film hydration technique strengthened the drug therapeutic action and reduced the side effects.[42] Solutol HS15 is the nonionic surfactant and tocopherol polyethylene glycol succinate (TPGS) is an FDA certified surfactant of polymer materials. Solutol HS15 and TPGS forming a block copolymer micelle that were applied by thin film dispersion method to prepare self-assembled micelles loaded with ginsenoside Rh2. The prepared micelles enhanced antitumor efficacy and solubility of Rh2.[99]

Liposomes are also considered as the useful carriers for the drug delivery. Methyl ether poly(ethylene glycol)-poly(lactide-co-glycolide) (mPEG-PLGA) nanoparticles loaded with Panax notoginsenoside were prepared using a water-in-oil-in-water double emulsion solvent evaporation method. These notoginsenoside-loaded core-shell hybrid liposomal vesicles resolved the restricted bioavailability of Panax notoginsenoside and enhanced its protective effects upon oral administration.[8]

Cholesterol, the crucial component of liposomes, could be replaced by ginsenosides. A ginsenoside Rh2-based multifunctional liposome system was developed while Rh2 functioning as both chemotherapy adjuvant and membrane stabilizer.[8] In another study, three different ginsenosides of Rh2, Rg3, and Rg5 were used for the formulation of a unique nanocarrier using thin-film hydration method. Beside long circulation in blood, paclitaxel encapsulated in these liposomal formulations could address active targeting through the significant suppression of gastric cancer tumor growth.[100]

7 | BIOMEDICAL APPLICATIONS OF GINSENG NANOPARTICLES

Several types of ginseng extracts, ginsenosides, and different ginseng nanomaterials are synthesized and studied for their biomedical applications. The list of nanoparticles and their biomedical applications were summarized in Figure 6. *P. ginseng* extracts such as root, leaf, and berry are used in the synthesis of gold, silver, and zinc nanoparticles that showed antioxidant, antibacterial, anticancer and anti-inflammation activity (Table 2). Ginseng nano formulations are broadly applied in drug delivery, testicular apoptosis, and anticancer activity (Table 2). Polymer based ginseng nanoparticles are widely used in the field of antitumor, cytotoxicity, drug delivery, and cerebral function (Table 2). Bone regeneration is also demonstrated by *P. ginseng* root extract within nanofibers and gelatin microspheres encapsulated with ginsenoside Rg1 (Table 2).

7.1 | Anti-inflammatory

The AuNPs synthesized using *P. ginseng* leaves inhibited the expression of mitogen-activated protein kinase (MAPK) and other inflammatory markers in a dose dependent manner through the blockage of p38 MAPK pathways. It can be a potent therapeutic target for inflammatory diseases.[104] Treatment of nontoxic AuNPs and AgNPs synthesized

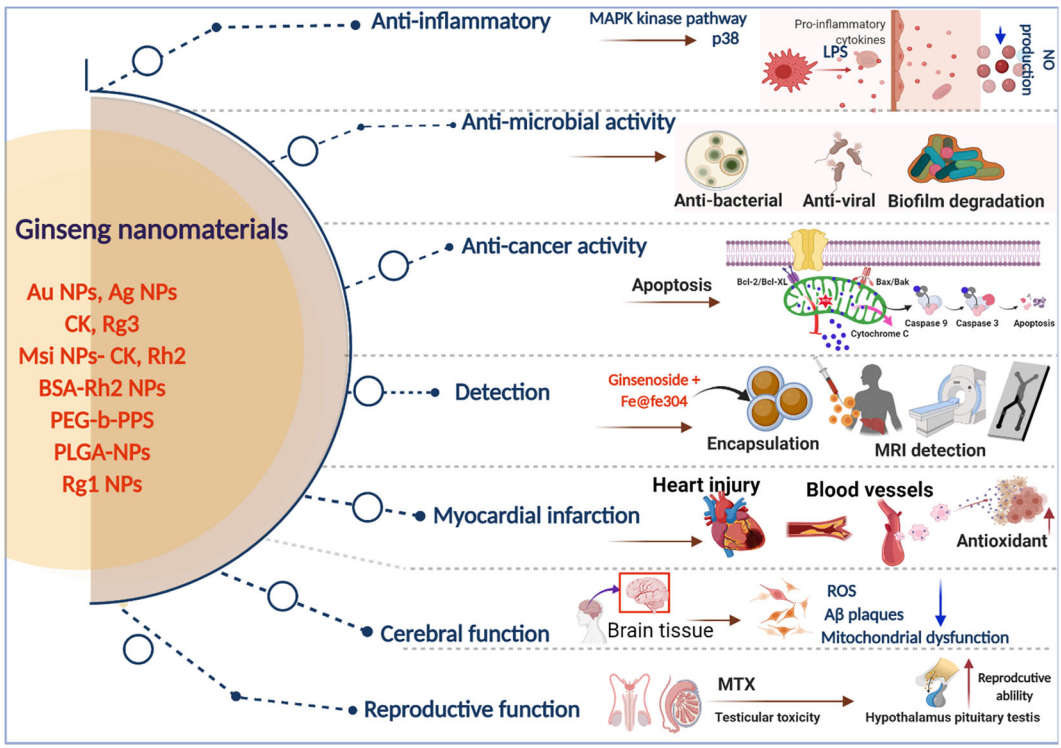

FIGURE 6 Various biomedical applications studied using ginseng nano-biomaterials. As explored in the review, the role of extensively studied ginseng-based nanoparticles for biomedical applications were highlighted in the figure. Aβ, beta amyloid; LPS, lipopolysaccharide; MRI, magnetic resonance imaging; MTX, methotrexate; NO, nitric oxide production; ROS, Reactive oxygen species. This figure was created using biorender software https://biorender.com/. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Synthesis and biological applications of ginseng nanoparticles.

Panax species	Plant parts	Ginseng secondary metabolites	Materials used	Synthesis method	Size (nm)	Shapes	Biomedical applications	Reference
Green synthesis								
P. ginseng (Black)	Root	-	Gold	Green	5	Icosahedral	Antioxidant/antibacterial	[45]
P. ginseng (Black)	Root	-	Silver	Green	8	Spherical	Anticancer	[45]
P. ginseng	Root	-	Silver	Green	5–15	Spherical	Anticancer/antiviral	[101]
P. ginseng	Root	-	Silver	Green	10–30	Spherical	Antimicrobial	[47]
P. ginseng	Root	-	Gold	Green	10–40	Spherical	-	[47]
P. ginseng	Root	-	Gold/Silver	Green	10–30	Spherical	Antibacterial	[102]
P. ginseng	Root	-	Gold	Green	16	Spherical	Antiproliferative	[46]
P. ginseng (Red)	Root	-	Gold	Green	-	-	Anti-inflammatory	[103]
P. ginseng	Dried root	-	Silver	Green	4–20	Distinct but mostly spherical	Detects Hg2+	[33]
P. ginseng (Red)	Dried root	-	Zinc	Green	-	Spherical/irregular	-	[6]
P. ginseng	Leaves	-	Gold	Green	-	-	Antioxidant/whitening	[25]
P. ginseng	Leaves	-	Silver	Green	-	-	Anticancer	[25]
P. ginseng	Leaves	-	Gold/Silver	Green	10–20/5–15	Spherical	Antimicrobial/anticoagulant/ biofilm inhibition	[48]
P. ginseng	Fresh leaves	-	-	Green	-	-	Anticancer/anti-inflammatory/ antiobesity	[5]
P. ginseng	Leaves	-	Gold	Green	-	-	Anti-inflammatory	[104]
P. ginseng	Berry	-	Silver	Green	10–20	Spherical	Antibacterial/anti-tyrosinase	[49]
P. ginseng	Berry	-	Gold	Green	5–10	Spherical	Antioxidant/antiaging/anti-tyrosinase/drug carrier	[49]
P. ginseng	Berry	-	Gold	Green	-	-	Antioxidant/antioxidant	[105]

TABLE 2 (Continued)

Panax species	Plant parts	Ginseng secondary metabolites	Materials used	Synthesis method	Size (nm)	Shapes	Biomedical applications	Reference
P. ginseng	Root	Rg3, Proteins, lipids and nucleic acids	Gold	Green	4.4 ± 1.0	Spherical	Immunomodulator	[51]
P. ginseng	-	Compound K	Gold	Green	-	Spherical/, Triangle/ Hexagonal	Nano-carriers	[52]
P. ginseng (Red)	-	Rg3	Gold	Green	4.7 ± 1.0	Spherical	-	[51]
Nano-formulation								
P. ginseng	-	Rb1	-	Green synthesis nanoformulation	100	-	Drug delivery	[106]
P. ginseng	-	Rb1/PPD		Nanoformulation	120	-	Anticancer/nano delivery	[29]
P. ginseng	-	ginsomes	-	Nanoformulation	70–107	Spherical	Increase immune response	[107]
P. ginseng	Root	-	-	Nanoemulsion	300 ± 50	Spherical	Testicular apoptosis	[77]
Microbial synthesis								
P. ginseng	-	CoPA3/Compound K	Gold	*Gluconacetobacter liquefaciens*	10–30	Spherical	Anti-inflammatory	[28]
P. ginseng		Compound K	Gold	*Lactobacillus kimchicus*	10-40	Spherical	Anticancer	[108]
Polymer based nanoparticles								
P. ginseng	-	Compound K	BSA	Green	30–50	Spherical	Drug delivery/anti-inflammatory/cytotoxicity	[109]
P. ginseng	-	Compound K	GC	Green	296, 255	Spherical	Anticancer	[89]
P. ginseng (Red)	-	Rg3	PEG/PPS	Green	-	Spherical	Inhibits myocardial ischemia injury	[9]
P. ginseng	-	Compound K	Carboxymethyl/ chitosan/calcium	Green	173.0 ± 0.71	Spherical	Inhibits cell proliferation	[86]

(Continues)

TABLE 2 (Continued)

Panax species	Plant parts	Ginseng secondary metabolites	Materials used	Synthesis method	Size (nm)	Shapes	Biomedical applications	Reference
P. ginseng	-	Rg3	Gelatin and HA	Electrostatic field	40 ± 5.8	Spherical	-	[93]
P. ginseng	-	Rg3	HA	Electrostatic field	31.2 ± 8.4	Spherical	Antitumor	[93]
P. ginseng	-	Rh2	BSA Nps	-	30–50	Spherical	Anticancer/anti-inflammatory	[82]
P. ginseng	-	Rg1	Biopolymer	-	79 ± 18	Spherical	Improves cerebral function	[110]
P. ginseng	-	FA-Rg5	BSA NPs	-	201.4	Spherical	Anticancer	[111]
P. ginseng	-	Rg3	Hybrid nano complexes	-	100–180	Spherical	Anticancer	[94]
P. ginseng	-	-	PLGA	-	-	-	Improves reproductive function	[112]
P. ginseng	-	25-OCH3-PPD	PEG-PLGA		43 ± 13	Spherical	Anticancer	[79]
P. ginseng	-	PPD a glycone	PEG		189 ± 15	Spherical	Cytotoxicity	[90]
P. ginseng		20(S)-ginsenoside Rg3	Co-polymers	-	90		Drug delivery/antitumor	[92]
P. ginseng	-	ANG-Rg3-NP	PEG-PCL	-	147 ± 2.7	Spherical	Inhibitory effect of glioma	[113]
P. ginseng	-	20s ginsenoside Rg3	BSA	-	179 ± 1.2	Spherical	Anticancer	[84]
P. ginseng	-	20 (R) ginsenoside Rg3	PLGA	Emulsion and solvent evaporation	97.5	Spherical	Antitumor	[78]
P. ginseng	-	Rb and Rg	Carbon nanotubes	-	-	-	Anticancer	[114]
P. ginseng	-	Rg3	Gold/heptaethylene glycol	-	4.4 ± 1.2	Crystal	-	[51]
P. ginseng	-	Rh2	Graphene oxide	-	-	-	Anticancer	[115]
P. ginseng	-	Rh2	20 (R/S)-Rh2- PEGA copolymer beads	-	-	-	Antitumor	[81]
P. ginseng	-	Compound K	Chitosan-calcium	Ion-cross linking method	173.2 ± 0.71	Regular and spherical	Antitumor	[86]

TABLE 2 (Continued)

Panax species	Plant parts	Ginseng secondary metabolites	Materials used	Synthesis method	Size (nm)	Shapes	Biomedical applications	Reference
P. ginseng	-	Rg3	PEG-Rg3-BSA	-	149.5	Spherical	Drug delivery, cancer therapy	[116]
P. ginseng	-	Rg3	PLGA-Rg3-Nps	Nanoemulsion	~100	-	Neuroprotective	[18]
P. ginseng	-	Ginsomes	GDNP	-	-	-	Immune response	[117]
P. ginseng	-	PPD	PEG-PPD	-	189	Spherical	Cytotoxicity	[90]
P. ginseng	-	Rg1	TfR targeted nanocarrier	-	122 ± 26	Spherical	Cerebral infarction	[110]
P. ginseng	-	Rg3, Rh2, Rg5, PTX	Liposome delivery	-	60.11 ± 3.42; 77.71 ± 3.22; 112.5 ± 4.1	Spherical	Antitumor	[100]
P. notoginseng	-	Rh2, PTX	Liposome delivery	-	99.03 ± 3.22	-	Antitumor	[118]
P. ginseng	Korean red ginseng extract		Titanium nanotube		-	-	Dental applications	[119]
P. ginseng	-	Rb1, Rg1	Carbon nanotubes	-	-	-	Anticancer	[114]
P. ginseng	Root	-	PCL nanofiber	-	-	-	Bone tissue engineering	[120]
P. ginseng	-	PPD	PCL	-	-	-	Antitumor	[121]
P. notoginseng	-	20(S)-Rg3	mPEG-b-PLGA	-	-	-	Postoperative peritoneal adhesion	[122]
P. ginseng	-	Rg3	Poly(L-lactide)	Electrospinning	-	-	Inhibits scar hyperplasia of skin	[123]
P. ginseng		Rg1	Strontium modified Ca2H2O9S2 Rg1 loaded gelatin microsphere	-	-	-	Bone regeneration	[124]
P. notoginseng		Novel panax notoginsenoside	PNS-HLV	-	337.8 ± 40.2	Spherical	Protects cerebral ischemia/reperfusion injury and myocardial ischemia	[8]

(Continues)

TABLE 2 (Continued)

Panax species	Plant parts	Ginseng secondary metabolites	Materials used	Synthesis method	Size (nm)	Shapes	Biomedical applications	Reference
P. ginseng	-	20(S)-Rg3	Ginsenoside Rg3/ PLGA fibers coated with HA	-	-	-	Repairs and inhibits hypertrophic scars	[125]
P. ginseng	-	Rb1	Ultra-small micelles	Film hydration	7.3 ± 0.1	Spherical	Improved corneal permeation/ anti-inflammatory	[42]
Chinese ginseng (*Rhizoma ginseng*)	-	Rh2	Mixed micelles	Thin-film dispersion method	74.72 ± 2.63	Spherical or spheroid	Antitumor	[126]
Miscellaneous								
P. quinquefolius	Root	Polysaccharides	-	Microfluidic process	20 ± 4	Spheres	Cancer/tumor detection	[127]
P. ginseng	Fresh root		Extracellular vesicles linked GDNP	Green	344.8	Spherical	Antitumor	[98]
P. ginseng	-	Rg3	Fe@Fe3O4	Microfluidic process	-	-	Antitumor	[26]
P. ginseng	-	Rg3	Fe@Fe3O4	Microfluidic process	8.2 ± 1.2	Crystalline	Anticancer	[10]
P. ginseng	-	CK and Rh2	Mesoporous SiNPs	-	200	Spherical	Anticancer/anti-inflammatory	[7]
P. ginseng	-	CK	SPION	Conjugation method	61.2 ± 1.2	Spherical	Anti-inflammatory	[58]
P. ginseng	-	Rg3	SPION	Conjugation method	68.3 ± 1.7	Spherical	Anti-inflammatory	[58]
P. quinquefolius	-	Polysaccharides	-	Microfluidic process	19	Spheres	Immunomodulatory/increased skin penetration	[13]
P. quinquefolius	-	Polysaccharide	-	Microfluidic process	20 ± 4	Spheres	Immunomodulatory/drug delivery	[96]
P. ginseng	-	Rh2	HA-ZnO	Co-precipitation method	-	-	Anticancer	[128]

Abbreviations: BSA, bovine serum albumin; $Ca_2H_2O_9S_2$, calcium sulfate hemihydrate; CoPA3, homodimeric α-helical peptide derived from coprisin; Fe@Fe3O4, iron oxide; GC, glycol chitosan; GDNP, ginseng derived nanoparticles; HA, hyaluronic acid; mPEG, methoxy polyethylene glycol; PCL, polycaprolactone electrospun; PEGA, amino polyethyleneglycol-polyacrylamide; PLGA, poly L-lactic-co-glycolic acid; PNS-HLV, panax notoginsenoside core-shell hybrid liposomal vesicles; PPS, poly propylene sulfide; SPION, super paramagnetic iron oxide nanoparticles; SiNPs, silica nanoparticles; TfR, transferrin receptors-targeting nanocarriers; ZnO, zinc oxide.

using *P. ginseng* leaves prompted dose-dependent repression of nitric oxide (NO) production induced by lipopolysaccharide (LPS) in RAW 264.7 cells[5] (Figure 6).

Comparing the cytotoxicity of microbial synthesized ginseng nanoparticles (GNP-CK-CopA3) in different cell lines including inflammatory murine RAW 246.7 cells, human dermal fibroblast cell lines NHDF, and HaCaTs, showed less to no cytotoxicity at 50 μg/mL.[28] Similarly, the microbial synthesized ginseng nanoparticles DCY51^T-AuCK NPs showed less or no toxicity toward murine RAW 246.7 cells at different concentrations.[108] The inflammatory response of murine RAW 246.7 cells is elevated by ROS from intracellular organs caused by cellular modification or other external factors. However, the localization of synthesized ginseng nanoparticles in cytoplasmic organelles including lysosome or mitochondria reduced the effect of LPS mediated ROS elevation.[28,108] Thus, ROS reduction was proved in murine RAW 246.7 cells following treatment with microbial synthesized ginseng nanoparticles.

The production of ROS, inducible nitric oxide synthase, and nitric oxide were significantly reduced by SPIONs conjugated with ginsenosides CK and Rg3 in LPS-activated RAW 264.7 murine macrophage cells in a dose-dependent manner.[58] Thus, these nanoparticles are non-cytotoxic to normal cells and can be used as a ginsenosides carrier for intracellular release in inflammatory diseases.

The higher anti-inflammatory efficacy of MSiNPs-CK and MSiNPs-Rh2 were shown in RAW264.7 cell lines as compared to ginsenosides CK and Rh2. Meanwhile, the superior biocompatibility in normal cell lines (HaCaT skin cells) and anticancer effect on A549 lung cancer, HepG2 liver carcinoma, and HT-29 colon cancer cell lines were shown at 10 μM concentration.[7] Improved stability and solubility of BSA-Rh2 nanoparticles significantly enhanced the therapeutic behavior of Rh2.[82] Therefore, BSA-Rh2 nanoparticles can be potentially used as a delivery vehicle for ginsenoside in inflammatory and cancer cell lines.

7.2 | Antitumor

The green synthesized AuNPs and AgNPs exhibited significant cytotoxicity to cancer cell lines including A549 lung cancer and B16B15 melanoma cell lines while no cytotoxicity to HaCaT skin and 3T3-L1 pre-adipocytes cells.[5] A novel extracellular vesicles-liked ginseng-derived nanoparticles (GDNPs) were isolated and characterized from *P. ginseng* C. A. Meyer. GDNPs can alter M2 polarization both in vitro and in vivo, which contributes to an antitumor response.[98] One-pot and facile fluorescent labeling of monodispersed ginseng polysaccharides derived nanoparticles (PS) was prepared from roots of *P. quinquefolium*. PS nanoparticles were successfully uptaken by the cells, sustained inside the cells (48 h), shown no tumor cytotoxicity, while it increased macrophage and nitric oxide production and thereby aid in therapeutic use of PS against tumor and cancer cells proliferation.[127]

The microbial synthesized ginseng nanoparticle DCY51^T-AuCK nanoparticles proved antiproliferative effect against various cancer cell lines including stomach, lung (A549) and liver (HT29) cancer cell lines through receptor-independent endocytosis.[108,129] In addition, photothermal effect of microbial synthesized CK loaded gold nanoparticle showed cancer cells lysis though elevated temperature induced by light energy conversion into hyperthermal heat.[108]

The Rb1/PPD nanoparticles exhibited high drug loading efficiency and capacity, appropriate size (~110 nm), long half-time in systemic circulation (nine-fold longer than free PPD), and higher accumulation at the tumor site. Thus, better antitumor efficacy in vitro and in vivo and reduced damage to normal tissues were demonstrated.[29] Ginsenoside Rb1 self-assembled with anticancer drugs produced stable nanoparticles with tumor inhibition and fewer side effects than that of free drugs.[130]

The encapsulation of ginsenoside Rg3 using PLGA also promoted its antitumor activity.[78] Ginsenoside GS25 encapsulated into PEG-PLGA nanoparticles for GS25 oral delivery improved anticancer efficacy, molecular targeting, and oral bioavailability.[79]

Greater in vitro therapeutic efficacy was found by bovine serum albumin-CK (BSA–CK) nanoparticles in HaCaT skin, HT29 colon cancer, HepG2 liver carcinoma, and A549 lung cancer cell lines in comparison with CK.[109] HSA, BSA, and bovine serum were used to reduce the cytotoxicity of Rh2 in HepG2 cells. HSA was suggested to enhance Rh2 water solubility, and thus it can be used as nanoparticles in Rh2 delivery process.[81] 20(s)-Rg3 loaded magnetic HSA nanospheres also increased the bioavailability and solubility of 20(S)-Rg3. Thus, it could efficiently induce apoptosis of HeLa cervical cancer cells when it combined with magnetic hyperthermia. Thermodynamic testing of 20(s)-ginsenoside Rg3-loaded magnetic HSA nanospheres showed that a specific concentration of magnetic fluid rosed at a steady temperature of 42–65°C.[84] Fe@Fe3O4 nanoparticles conjugated with ginsenoside Rg3 provide an antitumor therapy that inhibited metastasis and development of hepatocellular carcinoma through remodeling in vivo metabolism and unbalanced gut microbiota.[26]

Moreover, CK loaded cross-linked carboxymethyl chitosan calcium nanoparticles significantly enhanced cellular uptake and cytotoxicity of CK toward the PC3 cells, a model for the evaluation of cellular uptake and cytotoxicity in vitro.[86] Higher cytotoxicity in HT29 colon cancer cells was demonstrated by GC-CK conjugates than CK, while similar cytotoxicity was observed in HT22 mouse hippocampal and HepG2 liver carcinoma cell lines. However, remarkable cell viability was found in RAW264.7 cells treated with GC–CK.[89] Tumor proliferation was significantly inhibited by mPEG-b-P(Glu-co-Phe) copolymers co-loaded with Rg3 through decreased expression of proliferating cell nuclear antigen, resulting in tumor apoptosis via increased expression of caspase-3[92] (Figure 6).

The Rg3 monomer and HA-Rg3 nanoparticles alleviated the malignant behavior of H125 human non-small-cell lung cancer cells through the microRNA 192/tumor suppressor gene phosphatase and tensin homolog (PTEN) molecular axis, while better antitumor effect was shown by HA-Rg3 nanoparticles.[93] Nanocomplexes based on amphiphilic HACE and lipids (DSPE-PEG and PC) showed a sustained release of ginsenoside Rg3. In vivo clearance of (S)-Rg3 was also decreased by these nanocomplexes in rats. HACE-based nanoparticles move to the tumor region via passive and active targeting through the enhanced permeability and retention effect as well as HA–CD44 receptor interaction.[94] Thus, these hybrid nanocomplexes could be suggested as the good candidates for tumor targeting and delivery of anticancer agents. Ginsenoside introduced into nanostructured lipid carrier enhanced cytotoxicity, cellular uptake, and oral bioavailability of curcumin. Clinical outcomes in the treatment of colon cancer with similar genotype to HT29 can be improved by this strategy.[95]

Ginsenoside Rh2-mixed micelles also increased the solubility of ginsenoside Rh2 up to 150-folds compared to free Rh2, hence, improving the antitumor efficacy.[99] Rh2 liposome also prolonged the blood circulation and stabilized the structure of liposomes, while the paclitaxel-loaded Rh2 liposome realized the efficient tumor growth suppression.[118]

Graphene based water-soluble nanosheets including graphene oxide (GO) sheets are efficient drug delivery system.[131] Beside water dispersibility, GO sheet shows good biocompatibility, and it is also capable of targeted drug release in the acidic tumor microenvironment. GO itself disruptes glutathione biosynthesis and induces ROS accumulation in human cells. However, GO conjugated with the antioxidant ginsenoside Rg3, prior to loading with chemotherapy drug DOX, significantly reduced the toxicity of the GO carrier by abolishing ROS production.[132]

7.3 | Antimicrobial

Some of the known mechanisms involved in the antibacterial activity of nanomaterials are: (1) direct physical interaction of extremely sharp edges of nanomaterials such as graphene oxide nanowalls with cell membrane,[133,134] (2) ROS generation by nanomaterials for example by rGO under visible light,[135] and even by ZnO under dark condition,[136] (3) wrapping bacteria by nanomaterials such as graphene nanosheets,[137] (4) oxidative stress,[138] (5) reduction of nanomaterials such as graphene oxide to bactericidal graphene through the glycolysis process in the bacteria,[139] (6) DNA damage,[140] (7) ion release such as zinc from ZnO/GO composites,[141] and (8) electron capturing

from the respiratory chain of the bacteria by rGO, and transferring the trapped electrons into the O2 nanobubbles for ROS generation.[142]

The silver nanoparticles using 4-year-old fresh root extract of *P. ginseng* showed antimicrobial effect against pathogenic microorganisms[48] (Figure 6). The red ginseng root extract synthesized AgNPs exhibited antimicrobial activity against pathogenic microorganisms including *Vibrio parahaemolyticus*, *Staphylococcus aureus*, *Bacillus cereus*, and *Candida albicans*, while they exhibited biofilm degrading activity against *S. aureus* and *Pseudomonas aeruginosa*.[48] BG-AgNPs showed significant antibacterial activity against *Escherichia coli* and *S. aureus*.[45] Quasi spherical AgNPs using aqueous extract from *P. ginseng* roots showed virucidal against the influenza A virus.[53] The main mechanisms behind the antibacterial effect of ginseng extract synthesized NPs are explained as the biofilm inhibition activity,[48] free radical-scavenging activity,[45] and loss of permeability due to the structural changes in the cell membrane.[143]

Ginseng displayed antiviral effects by modulating both acquired and natural immunity. It is suggested as the potential therapeutic agent preventing SARS-CoV-2 infection along with the vaccine.[144] PEGylated nanoparticle albumin-bound-steroidal ginsenosides could treat symptoms such as coagulation, and cytokine storm that are associated with severe SARS-CoV-2 patients.[145]

7.4 | Detection

A simple, rapid, and miniatured portable system for the detection of Hg^{2+} in samples was designed using *P. ginseng* dried root powder.[33] The ginsenosides cross-linked with Fe@Fe3O4 nanoparticles are developed as the nanomedicine, enhanced magnetic resonance imaging, and auto-targeting in liver cancer therapy[10] (Figure 6). The PLGA-Rg3 nanoparticles were also offered as the theranostic material for encapsulating natural nutraceuticals for the treatment and detection of Alzheimer's disease.[18]

7.5 | Reproductive function

Testicular toxicity of methotrexate (MTX) is a clinically important adverse effect. Ginseng and ginseng nanoparticles alleviate MTX-induced testicular toxicity in rats, possibly by the inhibition of MTX-induced testicular apoptosis. The protective effect of ginseng nanoparticles showed better effect compared to the ginseng extract treatment.[77] Ginsenosides could also increase the reproductive function on the hypothalamus pituitary-testis axis when the *P. ginseng* formulated into the form of nanoparticles[112] (Figure 6). The adjuvant ginsenoside-based nanoparticles (ginsomes) could also promote subunit vaccine to induce a strong immune response and protective effects.[117]

7.6 | Cerebral function

Rg3-loaded PLGA nanoparticles showed improved biocompatibility, versatility, enhanced ability to cross blood-brain barrier, decreased Aβ plaques, ROS generation, reduced mitochondrial dysfunction and thus alleviates Alzheimer disease progression[18] (Figure 6). It was demonstrated that Rg1 nanoparticles could penetrate to brain tissue, stimulate neuronal recovery, and reduce the volume of cerebral infarction.[110,146] Furthermore, neural stem cells and their neural differentiation on graphene, and graphene-based neuronal tissue engineering can promisingly realize the regenerative therapy of various incurable neurological diseases/disorders and the fabrication of neuronal networks.[147]

7.7 | Myocardial infarction

Cardiac function was improved by intramyocardial injection of Rg3-loaded PEG-b-PPS nanoparticles while reducing the infarct size (Figure 6). Rg3 targets Forkhead box O3 (FoxO3a) protein that has anti-inflammatory, anti-fibrotic, and antioxidative functions.[9] Rg3 encapsulated pluronics F127 also enhanced the antioxidant effects in doxorubicin-induced heart injury model.[91]

7.8 | Antioxidant activity

P. ginseng leaves-mediated gold NPs exhibited antioxidant activity in a dose-dependent manner.[25] Ginseng berry AgNPs showed the highest free radical scavenging activity compared to ginseng berry AuNPs and ginseng berry extract.[49] The increased antioxidant activity of ginseng berry AgNPs could be correlated to the adsorption of bioactive compounds of extract over large surface area of spherical nanoparticles. Furthermore, the interaction of metal ions with plant metabolites within NP synthesis might result in improved free radical scavenging activity.

The increased free radical-scavenging activity of metal nanoparticles was attributed to the antioxidant activity of BG root extract. AuNPs and AgNPs biosynthesized using black ginseng root extract show promising prospect for the development of novel and biologically synthesized antioxidant agents.

8 | GINSENOSIDE BASED NANOPARTICLES DELIVERY

Most of the ginsenosides including Rh2, Rg3, CK, and Rg1 are the substrates for P-glycoprotein (P-gp) efflux transporters causing poor ginsenosides bioavailability.[17–20] Even, two ginsenoside isomers such as 20(S)-Rh2 and 20(R)-Rh2 exhibited significant difference in their cellular uptake due to the affinity and recognition difference between the two stereoisomers by efflux ABC transporters.[20] Nano-sized ginsenoside delivery system improved ginsenoside efficacy by penetrating to the cell to reach specific target sites and thereby increasing bioavailability. The list of transporters and transport mechanism of ginsenoside and ginsenoside nanoparticles were summarized in Figure 7. The use of novel multifunctional liposome delivery system successfully delivered ginsenosides (Rg5, Rg3, Rh2) through GLUT carrier-mediated endocytosis into gastric tumor sites. Ginsenoside Rg5 liposomes were transported through GLUT5 or GLUT2, ginsenoside Rg3 liposomes were mainly transported through GLUT1 and SGLT1, and Rh2 liposomes entered the cell mainly through GLUT1 transporters.[100]

Angiopep-2, kunitz domain-derived peptide from protease enzyme, is the specific ligand for low-density lipoprotein receptor-related protein-1 (LRP-1). Considering the overexpression of LRP-1 on glioblastoma or glioma cells and blood–brain barrier (BBB), angiopep-2 could be used for targeting brain.[148] Angiopep-2 eased the transport PLGA-Rg3 nanoparticles across the BBB from apical (blood/lumen) to basolateral side (brain) via a receptor mediated transcytosis.[18] Similarly, angiopep-2 functionalized ginsenoside Rg3 loaded nanoparticles crossed the BBB, enhanced the cellular uptake of nanoparticles, showed sustained drug release, and inhibited the C6 glioma cells proliferation dose-dependently.[113] On the other hand, development of poly-γ-glutamic acid-based nanoparticles loaded with Rg1 could successfully penetrate BBB via receptor mediated endocytosis and it could be a therapeutic agent for cerebral infarction treatment.[110] A transferrin targeted peptide conjugated with the nano-carrier wrapped Rg1 could also penetrate the BBB for treatment of cerebral infarction.[146]

Chitosan nanoparticles loaded with CK are transported into the cells through receptor mediated endocytosis and thus resulted in increased intracellular concentration of CK and achieved higher cytotoxicity due to nonrecognition of ginsenoside CK by P-gp efflux transporters.[87]

A folic acid modified BSA nanoparticles (FA-Rg5-BSA) has the ability to recognize folate receptor α (FRα) on cancer cells and eventually entered the target cells through receptor mediated endocytosis resulting in drug

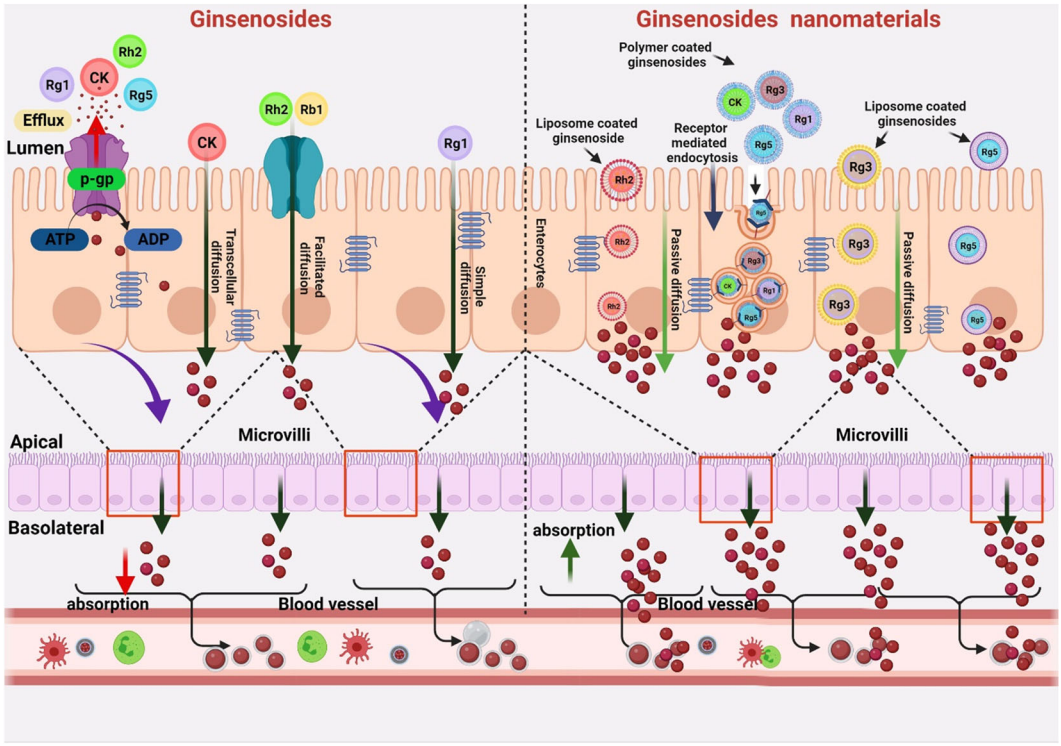

FIGURE 7 Ginsenosides and ginsenoside nanoparticles transport mechanism. In enterocytes, small amount (<5%) of CK, Rh2, Rb1, and Rg1 are transported through transcellular, passive, and simple diffusion. Ginsenosides such as Rg1, CK, Rh2, and Rg5 are the targets of efflux transporters, p-glycoprotein (P-gp) resulting in poor absorption of ginsenosides. Whereas, when ginsenosides coated with polymer or liposomes increased absorption of the ginsenosides through the receptor mediated endocytosis/transcytosis and passive diffusion. Based on the cited references in this review, we have created this figure using biorender software https://biorender.com/. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Targeted drug delivery using ginsenoside nanoparticles.

Ginseng metabolites	Synthesis	Target	Size (nm)	Reference
Rg3	Fe@Fe3O4-microfluidic process	Autonomous targeting for liver	8.2 ± 1.2	[10]
25-OCH3-PPD	PEG-PLGA	Tumor	43 ± 13	[79]
CK	Glycol chitosan	Tumor		[89]
PPD aglycone	PEG	Tumor	189 ± 15	[90]
Rg3	mPEG-b-P(Glu-co-Phe)	Tumor	90	[92]
Rg3	Hybrid nano complexes	Tumor	100–180	[94]
FA-Rg5	BSA	Tumor	201.4	[111]
Rg1	Transferrin receptor targeted nanocarrier	Brain	122 ± 26	[143]
CK	Carboxymethyl/chitosan/calcium	Tumor	-	[86]
Root	Polysaccharides-microfluidic process	Tumor	20 ± 4	[127]

Abbreviations: mPEG-b-P(Glu-co-Phe), PEG-block-poly (L-glutamic acid-co-L-phenylalanine); NPs, nanoparticles; PEG, polyethylene glycol; PLGA, poly L-lactic-co-glycolic acid.

accumulation on tumor sites, targeted delivery in cancer cells and reduced side effect in healthy cells.[111] Overall, these ginseng nanoparticles are proposed as the promising carriers for drug delivery to the brain and tumor sites (Table 3).

9 | CRITICAL PARAMETERS

9.1 | Size and time

Selection of organs for nanoparticle synthesis greatly affect the synthesis reaction time, nanoparticle size and it needs to be considered as one of the critical parameters when synthesizing ginseng nanoparticles using green methods. The size of various types of nanoparticles were summarized in Figure 8. So far, roots, leaves, and berries of *P. ginseng* have been extensively used for green synthesis. Fresh leaves mediated green synthesis of AgNPs is rapid, facile, stable, and cost-effective. Furthermore, it enhanced the pharmacological effect of nanoparticles probably due to the smaller size (10–20 nm) of synthesized nanoparticles compared to the nanoparticles synthesized using *P. ginseng* root (100 nm).[48] Compared to the fresh root and red ginseng powder, *P. ginseng* fresh leaves initiated rapid synthesis (3 min) of AuNPs and AgNPs (45 min).[48] Like leaves, fresh berry extract of *P. ginseng* synthesized smaller sized AuNPs (5–10 nm) and AgNPs (10–20 nm). The AuNPs and AgNPs synthesis using fresh berry extract were completed in 270 min and 24 h, respectively indicating that fresh samples initiate rapid synthesis compared to dried or root samples.[49] Therefore, use of fresh berry and leaves contribute to rapid, smaller sized nanoparticle synthesis and improved biomedical applications.

9.2 | Temperature

Temperature is considered as one of the important critical parameters when synthesizing nanoparticles using *P. ginseng* extracts. The synthesis of AuNPs and AgNPs using black *P. ginseng* root extract at 90°C significantly reduced the reaction time and the size of nanoparticles.[49] When the AuNPs and AgNPs were heated up to 700°C, there is complete degradation of organic compounds present in the *P. ginseng* leaves.[5] Certain ginsenosides are liable to changes in low pH and high temperature conditions. For instance, CK heated at 90°C for 3 h at pH 3 showed different bands of CK indicating the possibility of degradation at high temperature and low pH (3–5).[52,149] Therefore, optimum temperature for efficient synthesis of nanoparticles needs to be selected without affecting the pharmacological activity that is crucial for maintaining the bio-application.

9.3 | pH

The pH of nanoparticle is crucial to maintain stability, arrest aggregation of nanoparticles, and considered to be a significant factor when synthesizing metal nanoparticles. During the synthesis of silver and gold nanoparticles using *P. ginseng* fresh root, no shift in absorbance was observed even when a broad range of pH (3–12) was used denoting the stability and possible application in drug delivery.[47] One step green synthesis of AuNPs synthesized using Korean red ginseng roots also showed sustainable stability at pH 2–10 indicating phytochemicals coated well onto the nanoparticle surface and thus prevents the aggregation of nanoparticles.[46] Similarly, the use of *P. ginseng* leaves did not alter the stability of AuNPs and AgNPs at pH 3–12 even after a month of storage denoting the leaf extract itself acts as the reducing and stabilizing agents.[48] Meanwhile, a green synthesis of AgNPs using dried roots of *P. ginseng* showed pH dependent shift in nanoparticle formation. Alkaline pH (8–12) was more favorable than acidic pH (pH 6) in the formation of AgNPs using *P. ginseng* root.[33] Thus, use of fresh organs provided favorable environment to maintain stability of nanoparticles.

	Ginseng organ/secondary metabolites	Metals	Size	Charge
Green	Root [29]	Gold		NA
	Root [29]	Silver		NA
	Root [109]	Silver		NA
	Root [31]	Silver		NA
	Root [31]	Gold		NA
	Root [110]	Gold/Silver		NA
	Root [30]	Gold		NA
	Root [30]	Gold		NA
	Root [1]	Silver		NA
	Leaves [33]	Gold/Silver		NA
	Leaves [33]	Gold/Silver		NA
	Berry [34]	Silver		NA
	Berry [34]	Gold		NA
	Rg3 [35]	Gold		
	Rh2 [36]	Gold		
	CK [36]	Gold		
Nano-formulation	Rb1/PPD [65]	-		
	Rb1 [113]	-		
	Ginsomes [114]	-		NA
	Root [64]	-		NA
Microbial synthesis	CoPA3/CK [48]	Gold		NA
	CK [47]	Gold		
Polymer coated NPs	CK [96]	BSA		
	Rg3 [82]	Gelatin and HA		NA
	Rg3 [82]	HA		NA
	Rh2 [70]	BSA		
	Rg1 [100]	Biopolymer		
	FA-Rg5 [104]	BSA		
	Rg3 [83]	Hybrid nano complexes		
	25-OCH3-PPD [67]	PEG-PLGA		
	PPD [78]	PEG		NA
	Rg3 [81]	Co-polymers		NA
	ANG-Rg3 [103]	PEG-PCL		
	Rg3 [72]	BSA		NA
	Rg3 [66]	PLGA		
	CK [74]	O-carboxymethyl chitosan		
	CK [75]	Deoxycholic acid-O carboxymethyl chitosan		
	CK [77]	Glycol chitosan		NA
	Rg3 [11]	PLGA		NA
	Dried leaves [118]	HA-gold		NA
	PPD [78]	PEG		NA
	Rg1 [100]	Transferrin receptor targeted nanocarrier		
	PTX-Rg3 [90]	Liposome delivery		
	PTX-Rh2 [90]	Liposome delivery		
	PTX-Rg5 [90]	Liposome delivery		
	PTX-Rh2 [97]	Liposome delivery		
	Panax notoginsenoside [89]	Hybrid liposomal vesicles		
	Rb1 [25]	Ultra-small micelles		
	Rh2 [126]	Mixed micelles		NA
Miscellaneous	Root Polysaccharides [93]	Microfluidic process		NA
	Fresh root [87]	Extracellular vesicles linked Ginseng derived nanoparticles		
	Rg3 [44]	Microfluidic Fe@Fe3O4		NA
	CK and Rh2 [43]	Mesoporous silica nanoparticles		NA
	CK [46]	Super paramagnetic iron oxide		
	Rg3 [46]	Superparamagnetic iron oxide		
	Rg3 [45]	Microfluidic Fe@Fe3O4		

FIGURE 8 Size (nm) and surface charge (mV) of nanoparticles using different fabrication methods. Heatmap of size (nm) and surface charge (mV) of ginseng nanoparticles were constructed in Microsoft excel using conditional formatting option.

9.4 | Surface charge

The zeta potential of nanoparticles indicating their surface charge that is a critical factor determining the stability of nanoparticles dispersion. The different nanoparticles' zeta potential was summarized in Figure 8. Nanoparticles are stable when the absolute value of zeta potential is larger. The zeta potential of the bovine

serum albumin-compound K (BSA–CK) nanoparticles was −70.80 mV while it was highly stable.[109] The electrostatic repulsive force of the negatively charged nanoparticles prevents the nanoparticles from agglomeration and it could also give high stability to the colloidal solution.[58,109] It is also suggested that the interparticle interactions might partially contribute to the charge of Rb1/betulinic acid, Rb1/dihydroartemisinin, and Rb1/hydroxycamptothecine nanoparticles to be easily dispersed and resuspended after a period of sedimentation.[130]

The zeta potential of AuNPs-HEG-Rg3 was −4.12 mV while AuNPs itself had zeta potential of −18.25 mV.[51] Thus, it is suggested the contribution of HEG linker to the surface charge of final product by formation of steric layers, and thereby reducing the opsonization and aggregation of particles. However, the zeta potential of chitosan nanoparticles loaded with ginsenoside CK was roughly same as chitosan nanoparticles, demonstrating no significant difference of surface charge by encapsulation.[87] Meanwhile, due to the presence of many COO- groups in O-carboxymethyl chitosan, the zeta potential of the O-carboxymethyl chitosan nanoparticles was −14.6. After ginsenoside CK loading, nanoparticles showed stable dispersibility and the zeta potential was −29.6, that followed by a unimodal and concentric distribution.[86] The folic acid modification of Rg5-BSA nanoparticles also increased their negative surface charge from −14.9 to −22.5 mV, because after this modification the free amino groups are reduced.[111]

The negatively charged nanoparticles are generally internalized by clustering, then through the nonspecific binding with plasma membrane cationic sites, and their subsequent endocytosis.[150] The leaf extract AuNPs and AgNPs showed negative surface charge of −16.0 and −19.3 mV resulting in relative colloidal stability.[5] However, due to the positive surface charges on peptide-capped gold nanoparticles, they showed more internalization to the cells and prolonged intracellular retention in comparison with citrate-capped gold nanoparticles.[151]

It was shown that metal ions interacting with plant metabolites within formation of nanoparticles might improve the free radical scavenging activity of nanoparticles. Moreover, positively or neutrally charged AgNPs electrostatically attracting negatively charged phytochemicals act synergistically to improve the bioactivity of plants.[49]

It was demonstrated that the negative charge of Rg3 nanoparticles (−28.5 ± 2.5 mV) and angiopep-2 functionalized ginsenoside Rg3 loaded nanoparticles (−14.6 ± 3.2 mV) could prevent the plasma protein dilution and prolong the circulation time. While it could provide a better interaction with the cell membrane in vivo through the electrostatic repulsion.[152] Similarly, Rb1 and Rb1/PPD nanoparticles have negative surfaces charges due to the attached sugar residues on C-3 and C-20 of the PPD aglycone. While it could positively affect their interaction with the cancer cells.[29]

The zeta potential of nanoparticles increases when the nanoparticles enter an acidic tumor environment. It could affect the electrostatic interaction between the drugs such as Rg3 and Rg5 and nanoparticles, decreasing the stability of the nanoparticles, and thus resulting in drug release within tumor tissues.[92,111] Thus, the surface charge is a critical parameter affecting the stable dispersibility, circulation time, cellular internalization, and drug release of nanoparticles.

10 | PROSPECTS

In view of high demand for ginseng metabolites, and abundant distribution of Panax species around the world, further research should focus on other Panax species to unravel the exciting facts about the variation of age, organs, species specific nanoparticle synthesized for treating various diseases. This will further deepen the knowledge about the application of various types of Panax species in the nanomedicine era. Certain ginsenosides are heat unstable at high temperatures of synthesis and therefore it will be interesting to understand whether ginsenosides or other phytochemicals are responsible for the observed pharmacological effects. Further, it will be interesting to elucidate whether ginseng nanoparticle's cellular uptake reciprocate biomedical applications.

Compared to the dried extracts, fresh extracts provide efficient nanoparticle synthesis. The reason for the efficient green synthesis using fresh ginseng plant extracts should be addressed in the future. Even though metal nanoparticles synthesis using ginseng extracts is best, stable, and reliable method with least toxic effects in preliminary studies, there is a lack of sufficient evidence about their long-time exposure to the cells when treating health ailments. Therefore, more clinical studies are needed to investigate and optimize the efficiency of these nanoparticles in vivo. This can be addressed by exploring their toxicity, monitoring absorption, distribution, metabolism, and excretion, immunological response, and blood cell parameters of healthy subjects. Addition to that, bioavailability, and biocompatibility of ginsenoside nanoparticles are at the budding stage and therefore the involvement of respective ion channels and receptors for the delivery of ginsenosides to the target sites should be investigated in the future.

Moreover, inevitability and surplus successful microbial green synthesis approach yet to be discovered by utilizing various microbes as well as inorganic metal ions. Simultaneously, the precise mechanism of microbial synthesis nanoparticles is yet to be elucidated due to their distinct characteristic of microbial organism and physicochemical properties of metal ions including shape, size, surface modification and other environmental factors such as, temperature, pH, and pressure. Microbial mediated ginsenoside nanoparticle synthesis is emerging and therefore there is lack of sufficient reports on both intra- and extracellular synthesis of ginseng nanoparticles and their biomedical applications. It will be fascinating to explore the microbial mediated ginseng nanoparticle synthesis in the future.

Polymer-based ginsenoside nanocarriers have several beneficial characteristics including non-toxicity, biocompatibility, biodegradability, and cost-effective. Besides that, the possibility of engineering the polymer-based nanocarriers for targeting ability needs to be further investigated at in vitro and in vivo levels to achieve tissue-specific drug release, noninvasive systematic delivery, and ascertain noncytotoxicity toward any noncarcinoma cells. Furthermore, molecular docking studies can be used to elucidate the interaction between polymers and ginsenosides to ultimately elucidate their interaction sites and provide the optimal efficiency for ginsenoside nanocarriers.

Considering the facts about the high toxicity of anticancer drugs that seriously harm the organs, investigation of ginsenosides nanoparticles as an effective and biocompatible anticancer drugs or anticancer adjuvants holds good prospect. Selection of appropriate inorganic nanocarriers for the delivery of ginsenosides would be a remarkable step to deliver controlled release, high drug loading capacity, targeted delivery, photoimaging by incorporating fluorescence dye, and bio clearance of carrier thereby achieving enhanced efficacy of ginsenosides. Some applications of ginseng nanoparticles are limited including dental application, corneal and reproductive function (Figure 4, Table 2). Similarly, microbial based nanoparticle synthesis, nano emulsion, micelles, liposomes, nanotubes, microfluidic, and graphene-based ginseng nanoparticles are budding tools and need to be explored in depth to study their various biomedical applications.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no data sets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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