

Review

Recent Advances of Magnetic Gold Hybrids and Nanocomposites, and Their Potential Biological Applications

Gul Rehman Elmi^{1,2}, Kalsoom Saleem¹, Mirza Muhammad Faran Ashraf Baig³, Muhammad Naeem Aamir⁴, Minglian Wang^{5,*}, Xiuli Gao⁶, Muhammad Abbas^{1,*} and Masood Ur Rehman^{1,*}

- ¹ Riphah Institute of Pharmaceutical Sciences, Riphah International University, Islamabad 45320, Pakistan; dr.elmi707@gmail.com (G.R.E.); kalsoommohammed93@gmail.com (K.S.)
- ² Faculty of Health Sciences, IQRA University Islamabad Campus (Chak Shahzad), Islamabad 44000, Pakistan
- ³ Laboratory of Biomedical Engineering for Novel Bio-Functional, and Pharmaceutical Nano-Materials, Prince Philip Dental Hospital, Faculty of Dentistry, The University of Hong Kong, Hong Kong SAR 999077, China; faran@hku.hk
- ⁴ Faculty of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur 63100, Pakistan; naeem.aamir@gmail.com
- ⁵ Faculty of Environment and Life Science, Beijing University of Technology, Beijing 100124, China
- ⁶ Microbiological and Biochemical Pharmaceutical Engineering Research Center of Guizhou Province, State Key Laboratory of Functions and Applications of Medicinal Plants, School of Pharmacy, Guizhou Medical University, Guiyang 550025, China; gaoxl@gmc.edu.cn
- * Correspondence: mlw@bjut.edu.cn (M.W.); muhammad.abbas@riphah.edu.pk (M.A.); masood.rehman@riphah.edu.pk (M.U.R.)



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Abstract: Magnetic gold nanoparticles (mGNP) have become a great interest of research for nano-material scientists because of their significant magnetic and plasmonic properties applicable in biomedical applications. Various synthetic approaches and surface modification techniques have been used for mGNP including the most common being the coprecipitation, thermal decomposition, and microemulsion methods in addition to the Brust Schiffrin technique, which involves the reduction of metal precursors in a two-phase system (water and toluene) in the presence of alkanethiol. The hybrid magnetic–plasmonic nanoparticles based on iron core and gold shell are being considered as potential theranostic agents. In this critical review, in addition to future works, we have summarized recent developments for synthesis and surface modification of mGNP with their applications in modern biomedical science such as drug and gene delivery, bioimaging, biosensing, and neuro-regeneration, neuro-degenerative and arthritic disorders. This review includes techniques and biological applications of mGNP majorly based on research from the previous six years.

Keywords: nano hybrids; magnetic gold nanoparticles; nanocomposites; surface functionalization; core-shell nanocomposites; magnetic-plasmonic nanoparticles; biological applications

1. Introduction

The magnetic gold nanoparticles (mGNP) are hybrid metallic nanocomposites prepared from magnetic and plasmonic moieties that have attracted much attention over the last few years. Magnetic-plasmonic nanoparticles are basically core–shell structures with a bimetallic composition of iron (Fe), cobalt (Co), or nickel ferrite as the magnetic, core and gold (Au), platinum, or silver (Ag) as the plasmonic shell. However, magnetic-plasmonic core–shell structures based on magnetite (Fe₃O₄) or maghemite (γ-Fe₂O₃) core and Au shell offer renowned advantages, where the Au shell is coated over the Fe core in a controlled manner [1–3]. Core–shell nanostructures can also be based on Au and cadmium sulfide, and vice versa, to produce highly stable nanoparticles with semiconductor properties [4,5]. Several reducing and seeding agents are used to form a shell over the

core such as citric acid [6], sodium borohydride (NaBH_4) [7], sodium citrate [8], hydroxylamine [9,10], hydroquinone [11], L-ascorbic acid [12], N,N-dimethylformamide (DMF) and polyvinylpyrrolidone (PVP) [13].

The mGNP are synthesized in order to overcome limitations and/or to provide complementary modalities to individual iron oxide nanoparticles (IONP) and gold nanoparticles (GNP) to improve their biological applications [14,15]. In addition to stability and biosafety, mGNP can overcome several challenges of individual IONP and GNP including their optical characteristics (localized surface plasmon resonance and surface-enhanced Raman scattering), conductivity, bio-affinity via thiol/amine terminal group functionalization, and bioavailability, in addition to chemical stabilization of the magnetic core by preventing oxidation, corrosion and aggregation [1,16,17].

The mGNP can have several functionalities in a single hybrid nanocomposite structure because of the attachment sites for multiple functional groups. Surface functionalization of mGNP, especially with hydrophilic thiol groups, can render these hybrid nanoparticles more water-soluble and prevent the precipitation and aggregation of nanoparticles [18–20]. While synthesizing mGNP, their physicochemical parameters including size, morphology, surface charge, and thickness of Au shell must be precisely controlled to avoid their clearance via spleen, liver, and kidney and deliver them to a targeted site such as a tumor.

In addition to the surface modification, the combination of Fe based magnetic and Au based plasmonic materials will further explore biomedical applications for mGNP including targeted drug [21–23], DNA and siRNA [24–28], hyperthermia [10,29,30], drug solubility improvement [31], detection of protein biomarkers [32], PET-MRI (positron emission tomography-magnetic resonance imaging) contrast agents [33], and diagnostic or imaging applications for the diagnosis of tumor [19,31,34], and other diseases [35–37]. Furthermore, a magnetic field is developed by external magnets to deliver mGNP at a specific targeted site for the desired period as diagnostic or therapeutic agents followed by their eradication from the body. These processes can be observed by CT (computed tomography), MRI (magnetic resonance imaging), and other imaging methods [1,16,25,38].

Despite several advantages, researchers face challenges while synthesizing mGNP with a smooth, tunable, and complete Au shell. Several methods are being applied for the synthesis of mGNP but in this review, we will discuss the most effective, reliable, and commonly used techniques to synthesize mGNP with an effective Au shell. Furthermore, in this review, we will also discuss several biological applications of mGNP including diagnostic and therapeutic usage in the modern world. The techniques and biological applications of mGNP discussed in this review are majorly based on research over the previous six years.

2. Synthesis

Synthesis methods for metallic nanoparticles have been known for decades. After the synthesis of GNP through the reduction of Chloroauric acid (HAuCl_4) by Stevenson et al. in the early 1950s [39], there have been different methods reported, such as aerosol or vapor phase, gas deposition, and sol-gel techniques, for the synthesis of individual metallic nanoparticles. However, the synthesis of stable mGNP or magnetic-plasmonic nanoparticles with desired size and shape consisting of an inner Fe core and outer Au shell is difficult to obtain. A major challenge in synthesizing core-shell nanoparticles is to control uniformity and rate of coating to achieve bimetallic nanoparticles of similar size and shape. Another challenge in synthesizing bimetallic nanoparticles is obtaining the core-shell structure, specifically with Fe core and Au shell nanoparticles where Fe particles are water degradable and HAuCl_4 has strong oxidizing properties [40]. The most utilized techniques to obtain stable mGNP with desired properties for biological applications are coprecipitation, thermal decomposition, microemulsion, and Brust Schiffrin, as discussed below.

2.1. Coprecipitation Methods

Coprecipitation is a commonly employed method for the synthesis of mGNP. This is an aqueous-based technique utilizing metal precursors in a specific ratio followed by the addition of a base that precipitates out nanoparticles. The bases such as NH_4OH precipitate solution of ferric and ferrous salts or ferrous hydroxide suspension into nanoparticles that are being oxidized by oxidizing agents. The resulting magnetic nanoparticles (MNP) can be further subjected to surface functionalization to facilitate *in vivo* targeting or to improve the attachment of another species [15,38]. The coprecipitation technique is able to give higher quantities of MNP in less time, having strong magnetic properties with surface functionalization abilities and different shapes and sizes by adjusting the ionic strength, concentration of growth solution, and most importantly the pH. Agglomeration in a physiological and aqueous environment is the major challenge faced with MNP that can be overcome by immobilizing a positively charged polymer e.g., polyethylenimine, or the formation of the Au shell over MNP producing mGNP [15]. The proceeding method can be utilized for the synthesis of mGNP with or without the use of an intermediate layer between the Fe core and Au shell.

2.1.1. Coprecipitation Methods for mGNP with Intermediate Layer

The intermediate layer is also referred to as the “glue layer” that must have the ability to enhance the stability of IONP and provide binding sites for the attachment of GNP. Based on this purpose, the intermediate layer can be between the IONP and GNP or cover the core-shell nanostructure as shown in Figure 1. The materials for the glue layer or intermediate layer between the core and shell of mGNP can be polymer, carbon, or another metal i.e., silica [17,20,38]. The silica, being a common choice, is biocompatible, helps in the internalization of mGNP into the cells, and provides functionalization of surface functional groups. Silica aids in the seeding of small GNP onto the surface of MNP and helps in the reduction of the Au layer [38]. A variety of mGNP were synthesized using silica as the intermediate layer. Raspberry structured mGNP with loaded curcumin were synthesized, where MNP were produced by precipitating $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ in the presence of sodium hydroxide (NaOH) to provide pH 10 for 30 min. The Stober synthesis approach was employed for the addition of a silica layer followed by its surface modification with the help of 3-aminopropyl) triethoxysilane (APTES). The APTES helps in the salinization/functionalization of silica surface to facilitate the attachment of Au [41]. GNP were adsorbed onto the surface of resultant $\text{MNP}@SiO_2@APTES$ nanoparticles by rendering the surface of $\text{MNP}@SiO_2@APTES$ nanoparticles more positive with the help of phosphate buffer solution. Curcumin was loaded onto mGNP followed by PEGylation to improve circulation time in blood [38,42,43].

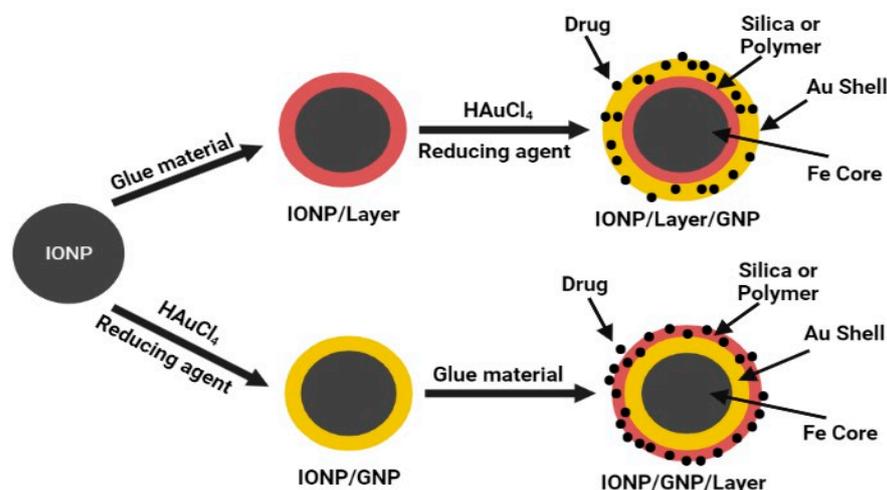


Figure 1. Schemes of synthesizing magnetic gold nanoparticles with intermediate layer.

Polymers have been used for the fabrication of mGNP to impart stability [44] and conduction property [16] with the formation of a homogenous layer around the core. Polypyrrole (PPy) is an important conductive polymer used for many biological purposes and the induction of photothermal effects. Feng et al. utilized PPy as an intermediate layer (Figure 2) in magnetic gold nanorods (mGNR), where, gold nanorods (GNR) were obtained from a modified seed technique utilizing hexadecyltrimethylammonium bromide (CTAB) modified Au seeds synthesized by reduction of HAuCl_4 with NaBH_4 and a growth solution containing AgNO_3 , CTAB, HAuCl_4 , and ascorbic acid. The GNR were coated with PPy using iron cation mediated oxidation polymerization where the abundance of Fe^{2+} and Fe^{3+} ions lead to the formation of dark PPy coated GNR that was subjected to synthesize mGNR ($\text{Au@PPy@Fe}_3\text{O}_4$) by diluting with ethanol and water in the presence of NH_4OH to precipitate IONP. The IONP adhered electrostatically to the PPy covering on GNP [16].

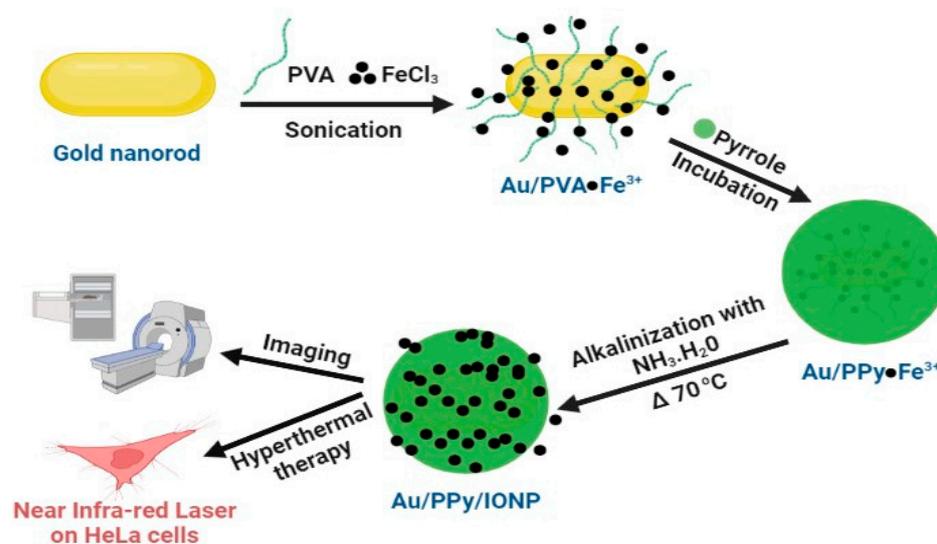


Figure 2. Synthesizing scheme for mGNP using polypyrrole as intermediate layer.

The products from aqueous-based synthesis approaches provide a streamlined synthesis of mGNP for biological applications where only non-toxic and biodegradable reagents, polymers, and other materials are used throughout the preparation processes instead of organic solvents. The mGNP were synthesized using PVP as an intermediate layer between IONP core and the plasmonic GNP shell by an aqueous-based synthetic method at room temperature [44]. PVP is a biodegradable, non-ionic, and non-toxic polymer used for several biological purposes and to stabilize MNP [45]. For $\text{Fe}_3\text{O}_4/\text{PVP}/\text{Au}$ nanocomposite [46], IONP were prepared by precipitation of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ in the presence of NaOH solution. The black color IONP were redispersed in PVP solution for coating and stabilization. Finally, $\text{Fe}_3\text{O}_4/\text{PVP}/\text{Au}$ nanocomposites were synthesized by assembling Au seeds, prepared by HAuCl_4 reduction using NaBH_4 and hydroxylamine hydrochloride with the help of CTAB, around PVP-coated IONP through electrostatic interaction. Xie et al. [44] also used PVP as intermediate layer to stabilize IONP and aided in attachment of GNP via electrostatic interaction to produce mGNP by coprecipitation technique.

Furthermore, Polyethyleneimine (PEI) is a biocompatible and non-toxic polymer that can reduce and stabilize the Au shell over IONP [45,47]. Panday et al. [25] synthesized PEI coated mGNP for intracellular delivery of siRNA in prostate cancer (PC3) cells, where, iron chloride salts were coprecipitated in presence of ammonia to produce IONP and coated with Au using sodium citrate to reduce Au^{3+} to Au^{1+} and Au^0 . The resultant hybrid nanoparticles with coated PEI followed by conjugation of carboxyl groups of hyaluronic acid (HA) to amino groups of PEI via the formation of amide bonds. In another study [48], PEI was employed in the formulation of multifunctional mGNP for delivery of doxorubicin (DOX), where tumor specificity was enhanced by the use of magnetic

property and bevacizumab, a humanized monoclonal antibody. They synthesized IONP by coprecipitation of FeSO_4 in the presence of KNO_3 and NaOH followed by multiple coating with PEI and poly (styrenesulfonate) (PSS). The polymer-coated IONP were further coated with GNP by the reduction of HAuCl_4 by NaBH_4 . Ahmed et al. [49] Fe_3O_4 -Au-PEI core-shell magneto-plasmonic nanocomposite were prepared by a coprecipitation technique that had iron oxide induced supermagnetic properties and showed more targeted intracellular uptake in human liver cancer cell line (HepG2).

In research by Pati et al. [50] chitosan was utilized for surface modification of IONP and helped in the attachment of the Au layer to form mGNP. In their work, they synthesized oleic acid-coated IONP by coprecipitation of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ in NaOH solution followed by the addition of oleic acid. The product was subjected to surface functionalization by chitosan and attachment of GNP with the help of NaBH_4 to produce $\text{Fe}_3\text{O}_4@ \text{Chit} @ \text{Au}$ hybrid mGNP which were separated from the mixture by a magnet. In another study [51], the same methodology was utilized to produce mGNP introducing chitosan as an intermediate layer and using hydroxylamine hydrochloride as a reducing agent for GNP over the chitosan layer, where, the untreated GNP were removed by using a magenta separation technique.

2.1.2. Coprecipitation Methods for mGNP without Intermediate Layer

The mGNP without the intermediate layer is known as the direct coating and involves the formation of an Au shell over a magnetic core in the aqueous or organic phase. The surfaces of direct coated mGNP are mostly altered with a polymer or capping agent for the attachment of drugs. These capping agents can be a reducing agent or an additional material used in the formulation, as described earlier [1,15]. The active drug is incorporated into coprecipitated direct coated mGNP by the drug's attachment to the Au layer via electrostatic interaction. For example, Elbially et al. [23] synthesized IONP by precipitating chloride salts of Fe in the presence of ammonia solution and sodium citrate at 90°C . IONP was added to a boiled solution of HAuCl_4 for synthesizing mGNP that were coated with thiolated-PEG. DOX was attached to the PEGylated mGNP surface via electrostatic interaction to form mGNP-DOX conjugates. Moreover, dynamic light scattering (DLS) and transmission electron microscopy (TEM) analysis were carried out showing the diameter of mGNP as 29 and 24 nm, respectively, with high colloidal stability and photostability as shown in Table 1. These multifunctional conjugates were effective for interstitial photothermal therapy due to Au shell and targeted drug delivery being provided by magnetic core using external magnets. PEGylated mGNP can be used as an effective contrast agent for MRI and other diagnostic purposes.

Fe_2O_3 core and Au shell nanoparticles were synthesized by employing the coprecipitation technique with subsequent oxidization by nitric acid (HNO_3) [52]. They first produced MNP by precipitating $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ in NaOH solution with vigorous stirring to reduce ferric ions to Fe_3O_4 magnetic particles as black precipitates that were subjected to oxidization by HNO_3 resulting in colloidal solution of Fe_2O_3 particles as reddish-brown. Fe_2O_3 nanoparticles were formed by tetramethylammonium hydroxide (TMAOH) solution at $\text{pH} = 12$. TMAOH dissociation was responsible for linking surfaces of Fe_2O_3 nanoparticles due to the release of $\text{N}(\text{CH}_3)^+$ and OH^- ions. Finally, Fe_2O_3 core and Au shell nanoparticles were synthesized by seeding process utilizing an excess of colloidal solution of Fe_2O_3 nanoparticles and slow addition of HAuCl_4 and $\text{NH}_2\text{OH} \cdot \text{HCl}$.

In a study by Chen et al. [53] mGNP were produced by coprecipitation of an aqueous solution of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ in ammonia solution to form IONP followed by its coating with GNP using sodium citrate to reduce HAuCl_4 boiled in aqueous solution. The Au shell formation over the magnetic core as indicated by a change from a brownish color to burgundy. Sodium citrate formed capping around mGNP with enhanced stability and avoidance of aggregation [15]. Hot citrate reduction was first reported by Lyon et al. [54], where some experimental conditions such as concentration of reducing agent, the ratio of IONP, and Au precursor can affect the formation of Au layer over magnetic nanoparticles.

Fantechi et al. [9] prepared Au-Fe nanocomposites by preparing ultrasmall IONP by coprecipitation of $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in the presence of ammonia solution, followed by a coating of GNP with the help of hydroxylamine being used as reducing agent. In another study [55], spiky magnetic gold supraparticles were synthesized using the coprecipitation method to prepare IONP followed by the formation of a smooth layer of Au to produce mGNP. Magnetically separated smooth surface mGNP were converted to a spiky surface using an aqueous solution of hydroquinone as a reducing agent to seed more GNP over previously prepared smooth surface mGNP. The spiky mGNP can be useful for multiple applications including targeted drug delivery, catalysis, surface enhanced raman spectroscopy (SERS) biosensing and magnetic separation.

The mGNP were developed by Hao et al. [56] for targeted delivery of fluorescein isothiocyanate (FITC) into KG-1 cells. They synthesized IONP by precipitating an acidic solution of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in presence of NaOH. Then a mixture of HAuCl_4 and sodium dodecyl sulfate solution (SDS), as stabilizer surfactant, were sonicated with IONP, where, Au^{3+} were reduced with help of ascorbic acid followed by the addition of HCl solution to form a layer of GNP over IONP. Finally, mGNP were functionalized with HS-PEG- NH_2 for attachment of FITC.

Table 1. Size and stability analysis of magnetic gold nanoparticles synthesized via various methods.

mGNP and Method	Size	Stability	References
PEGylated mGNP ¹ -DOX ² (Coprecipitation method)	TEM ³ shows size of 10 nm and 24 nm for MNP ⁴ and mGNP, respectively, with thickness of gold shell about 11–15 nm. DLS ⁵ indicated diameter of MNP and mGNP as 12 ± 3 nm and 29 ± 4 nm, respectively, being consistent with results of TEM.	In Vitro stability depicted mGNP as highly stable at 4 °C with homogeneity and dispersity. Photothermal response of mGNP was photostable during temperature elevation via irradiation for 30 min.	[23]
Au-Fe Janus mGNP (Thermal decomposition method)	Sizes of two different MNP were observed via TEM as ~16 nm and ~20 nm. Effect of gold nanostar growth on MNP was observed for Janus mGNP as 16.25 nm and 20.41 nm, respectively.	Janus mGNP were functionalized with 4-MBA ⁶ and thiol terminated PEG ⁷ to enhance colloidal stability in water, PBS and cell media. Also, high gold to iron ratio was significant for MR ⁸ and CT ⁹ imaging.	[57]
Fe/Au immobilized on PE ¹⁰ (Microemulsion method)	Diameter of mGNP were ~10 nm with magnetic core of 8 nm and gold shell of 2 nm.	Colloidal stability was increased by immobilization of mGNP on PE foils.	[58]
Fe/Au mGNP (Brust Schiffrin method)	mGNP with 5 to 100 nm size and high monodispersity were obtained.	During thermally activated protocols, for purpose of formulation development, size of MNP and GNP ¹¹ were raised from 4.4 to 4.5 nm and 2 to 6.4 nm, respectively, indicating coalescence and growth of GNP.	[59]

mGNP¹: magnetic gold nanoparticles; DOX²: doxorubicin; TEM³: transmission electron microscopy; MNP⁴: magnetic nanoparticles; DLS⁵: dynamic light scattering; 4-MBA⁶: 4-mercaptobenzoic acid; PEG⁷: polyethylene glycol; MR⁸: magnetic resonance; CT⁹: computed tomography; PE¹⁰: polyethylene; GNP¹¹: gold nanoparticles.

2.2. Thermal Decomposition Techniques

Thermal-based synthesis can be solvothermal synthesis (organic-based solvent) and hydrothermal synthesis (water-based solvent) [60]. The thermal decomposition technique is applied to synthesize monodisperse MNP, where, organometallic precursors, for example, metal acetylacetonates ($\text{Fe}(\text{acac})_3$) and metal carbonyls ($\text{Fe}(\text{CO})_5$) or another organometallic precursor, is heated often around 300 °C temperature with stabilizing surfactant in the organic solvent. The resulted products with highly crystalline nature and monodisperse MNP qualify these methods for common usage [38,61].

The thermal decomposition technique can be a one-pot and two-pot synthesis technique for the preparation of nanodimers or mGNP [3]. In a one-pot synthesis approach, the iron salts at 150 °C and Au precursor (HAuCl₄) at 120 °C are mixed together and their temperature is raised to 300 °C resulting in the decomposition of Fe(CO)₅ or Fe(acac)₃ and HAuCl₄ followed by few more steps and leading to the formation of mGNP in an easy way. While, in the two-pot synthesis approach the iron salts at 150 °C are introduced to a mixture of pre-synthesized GNP and oleic acid, 1-octadecane with oleylamine followed by raise in temperature until 300 °C.

Peng et al. explained the principle for the formation of IONP earlier by this technique using Fe(CO)₅ as metallic core and oleylamine as capping agent. They prepared MNP of <10 nm diameter with narrow size distribution. Therefore, this technique is more favorable because it gives MNP stability, controlled size, and morphology with more yield. The major drawback with the thermal decomposition technique is the usage of the dispensability of resulting MNP in organic solvents only, which requires additional modification at the surface to make aqueous soluble [15,62]. Similar to the coprecipitation technique, this technique can also be utilized to produce mGNP with or without an intermediate layer.

2.2.1. Thermal Decomposition Techniques for mGNP with Intermediate Layer

The intermediate layer can be silica or polymer for the purpose of surface functionalization and to render the resultant mGNP soluble in the aqueous phase for their applicability in respective biomedical applications [38,63]. Fantechi et al. produced flower-like heterostructured mGNP applying silica as an intermediate layer by thermal decomposition technique for two precursors, Fe(acac)₃ and Fe(CO)₅, separately with different reaction conditions at 315 °C temperature for 2 h and 50 min, respectively. They utilized preformed oleylamine-capped GNP in reaction mixtures. Finally, both the flower-like heterostructured mGNP were coated with silica as the final coating to render them water-soluble for biomedical applications [63].

Kostevsek et al. [64] demonstrated the use of acetylacetonates in the thermal decomposition technique. They prepared multimodal FePt/SiO₂/Au nanoparticles by this method. Where, FePt core nanoparticles were prepared by heating a mixture of Fe(acac)₃, Pt(acac)₃, benzyl ether, oleylamine, and oleic acid at 200 °C for 30 min followed by 280 °C for a further 30 min. These nanoparticles were coated with silica with APTES induced surface functionalization to add a layer of GNP using NaBH₄ as a reducing agent. The FePt magnetic-plasmonic alloy provided more magnetization to mGNP compared to iron oxide only. The synthesized mGNP had strong photothermal antitumor effects with ease of manipulation with the external magnetic field.

In another study [65], multifunctional mGNP were synthesized by mentioned method for photothermal cancer therapy guided by MRI. They prepared IONP by heating a mixture of Fe(acac)₃, benzyl ether, and oleylamine to 300 °C followed by their coating, for functionalization purposes to obtain surface amino groups, with a positively charged organic/inorganic hybrid silica layer to form Fe₃O₄@T-Si nanocomposites. Finally, mGNP were synthesized by the electrostatic adherence of Au seed to the silica layer of previously prepared IONP using NaBH₄ as a reducing agent. These mGNP were formulated as nanorattles using potassium carbonate for biomedical applications.

Different polymers including PEI, PVP and PEG can be incorporated as intermediate layer by thermal decomposition technique, which mostly employs the aqueous phase during synthesis as an added advantage. PEI [45,47], being a biocompatible and non-toxic polymer that can reduce and stabilize Au shell over IONP, can be incorporated as an intermediate layer by the thermal decomposition technique. Lee et al. [66] prepared multifunctional mGNP with magnetic and optical properties. They synthesized PEI-coated IONP by stirring the mixture of FeCl₃·6H₂O in ethylene glycol, sodium acetate anhydrous and PEI for twenty minutes at 60 °C followed by a heating decomposition reaction at 220 °C for 2 h in a home-made autoclave. Then, mGNP were prepared through the development of electrostatic interaction between negatively charged GNP and positively charged PEI. In

another study [67], mGNP were synthesized from PEI coated IONP cluster, produced via thermal decomposition reaction, and GNP using ascorbic acid as a reducing agent. The resultant mGNP were magnetically guided for photodynamic and photothermal therapies.

The mGNP with polymer as an intermediate layer through thermal decomposition reaction can also be synthesized by the microwave method as demonstrated by Yu et al. [68] who formulated mGNP by using the microwave as the heat source. They synthesized PVP-coated IONP by aqueous-based reaction in benzyl alcohol where microwave was used throughout the process followed by their dispersion in ethylene glycol solution of PVP again and HAuCl_4 in presence of microwave to produce mGNP. The PVP was used as a coating material for both IONP and GNP separately for the purpose to stabilize and shape nanoparticles in addition to their property as a mild reducing agent.

PEG is a biocompatible polymer that can help in the formation of desired or novel morphology with the capability to provide ease of surface functionalization [3]. In a study [69], PEG was employed to produce Trisoctahedral mGNP where IONP were synthesized by thermal composition reaction of $\text{Fe}(\text{acac})_3$ and oleic acid in presence of organic solvents. Further, the PEG layer was obtained via ligand exchange method to prepare hydrophilic IONP followed by their coating with poly-L-lysine that will help in the growth and seeding of the trisoctahedral Au shell. Finally, mGNP were coated with silica to attach DOX and oligonucleotides (dsDNA) to get near-infrared (NIR) light-responsive and magnetically targeted theranostic mGNP.

2.2.2. Thermal Decomposition Techniques for mGNP without Intermediate Layer

The simpler method involves the thermal decomposition of magnetic and plasmonic moieties separately or together. Thermal decomposition reaction for synthesizing mGNP without an intermediate layer can be induced by utilizing a microwave or autoclave as a heating source. For example, Le H. et al. [8] well demonstrated microwave as a heating source to synthesize mGNP without an intermediate layer through simultaneous thermal decomposition reaction of Fe and Au precursors. They prepared mGNP by stimulating the thermal decomposition reaction of 1-methyl-3-hexyl imidazole FeCl_4 and HAuCl_4 in the presence of sodium citrate as a reducing agent using a microwave oven. Resultant magnetic ionic liquid/gold nanoparticles were successfully prepared as ultrasensitive SERS substrates to detect clopidol, an effective anti-coccidiosis drug.

Another way to achieve mGNP without an intermediate layer is the use of the solvothermal method where decomposition or chemical reaction is induced to precursors in a closed system under high pressure and temperature [70]. The principle of decomposition reaction induced via the solvothermal method was evidenced by some researchers via preparing magneto-plasmonic nanoassemblies. The mGNP were synthesized by a heating mixture of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, sodium acetate, and gelatin in ethylene glycol at $200\text{ }^\circ\text{C}$ for 6 h in a Teflon-lined stainless-steel autoclave to induce a decomposition reaction to formulate Fe_3O_4 nanoclusters. After cooling, an Au shell was produced over IONP using HAuCl_4 and tetrakis-hydroxymethylphosphonium chloride (THPC) to induce Au seeds. Resultant mGNP were PEGylated to enhance in vivo circulation and render them biocompatible [71].

Reguera et al. [57] produced Janus magnetic Fe_3O_4 -Au dumbbells by simultaneous heating of $\text{HAuCl}_4 \cdot 3\text{H}_2\text{O}$ and $\text{Fe}(\text{CO})_5$ in 1-octadecane and oleylamine. Two different size Fe_3O_4 -Au dumbbells (with 16 nm and 20 nm, iron oxide) were synthesized by heating variable quantities of precursors up to $300\text{ }^\circ\text{C}$ and $310\text{ }^\circ\text{C}$, respectively, followed by their exposure to air for 30 min for oxidation of Fe. The effect of gold nanostar growth on the size of MNP was also determined. Colloidal stability of Janus mGNP were improved via functionalization with 4-mercaptobenzoic acid and thiol terminated PEG as discussed in Table 1. The Fe_3O_4 -Au dumbbells with interested morphologies were obtained via further Au^{3+} ions reduction on the surface of nanoparticles by using PEG and DMF. During the initial synthesis, oleylamine will act as a reducing agent [15].

2.3. Microemulsion and Reverse Micelle Method

Another method for the formation of the bimetallic metallic core and plasmonic shell nanoparticles is the microemulsion technique, sometimes also called as reverse micelle method, which aids in Au shell formation by bringing the IONP and GNP together to synthesize spherical and cubic shaped mGNP with narrow size distribution [40]. This technique utilizes two different approaches, including the W/O and O/W microemulsion, consisting of a water-based mixture of HAuCl_4 , FeCl_3 , and FeCl_2 and an organic solvent-based mixture of surfactants, PVP or CTAB. Generally, IONP are precipitated inside micelle by rendering the pH of mixture alkaline via NaOH solution followed by the formation of Au shell over IONP through the addition of NaBH_4 to reduce HAuCl_4 [1,15].

This technique was first introduced in the 1980s for the synthesis of various metallic nanoparticles including rhodium, palladium, and platinum nanoparticles [72]. Recently, in a study, mGNP were synthesized utilizing the microemulsion technique [73]. They prepared IONP by formulating two microemulsions as indicated in Figure 3. The first microemulsion was prepared by the addition of an aqueous phase containing FeCl_3 and FeCl_2 to the organic phase of toluene containing CTAB as a surfactant to stabilize the microemulsion. The second microemulsion was a mixture of ammonium hydroxide solution and solution of CTAB in toluene. Subsequently, after mixing two microemulsions, IONP are homogenized together at $50\text{ }^\circ\text{C}$ with a constant flow of N_2 gas for 60 min. Magnetically separated IONP were Au coated by dropwise addition of HAuCl_4 dissolved in chloroform and oleylamine into IONP solution. Finally, MUC-1 aptamer conjugated mGNP were synthesized for the eradication of breast cancer cells through photothermal therapy.

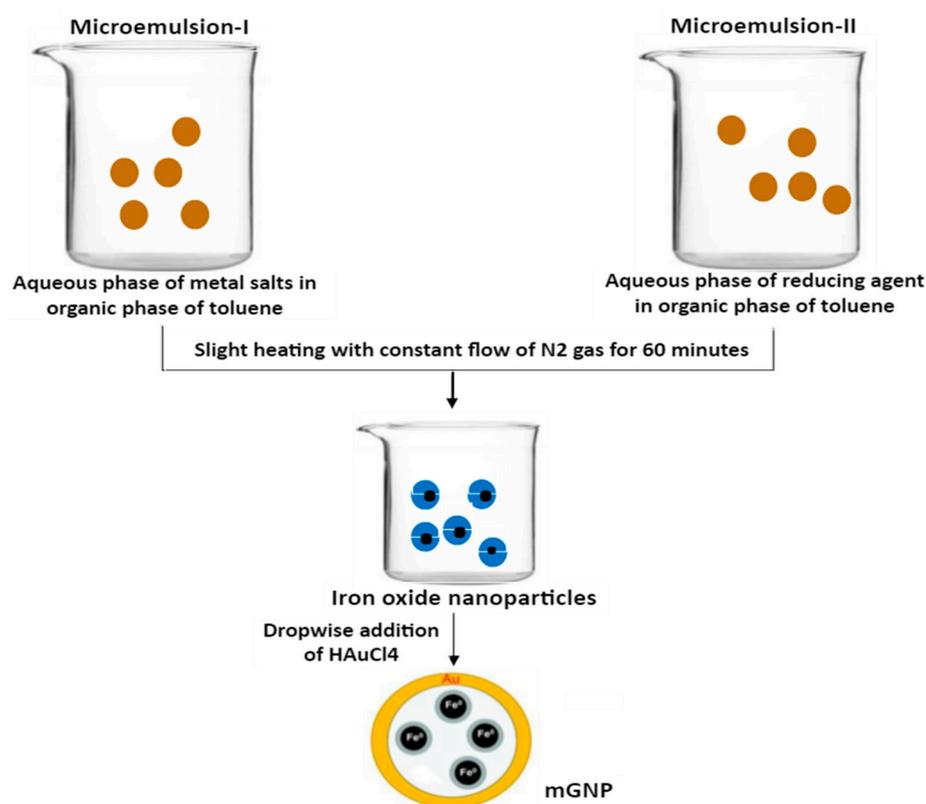


Figure 3. Schemes of synthesizing magnetic gold nanoparticles by microemulsion technique.

In another study by Kvitek et al. [58] reverse micelle or microemulsion technique was utilized for the synthesis of colloidal mGNP with $\sim 10\text{ nm}$ size (Table 1) of magnetic Fe core and Au shell using CTAB in n-octane in the oil phase. N-butanol was utilized as a co-surfactant to facilitate further stabilization of micelle solutions. Aqueous phases containing HAuCl_4 and FeSO_4 were separately prepared, each with NaBH_4 . Finally, con-

trolled size mGNP were produced by making micelles through mixing aqueous and oil phases, and nanoparticles were precipitated out followed by surface functionalization of Au shell with thiol groups for immobilization on plasma-treated polyethylene surface. Azhdarzadeha et al. [10] also prepared actively targeted theranostic mGNP, where, IONP were synthesized through the utilization of microemulsion principle followed by their oxidation for 30 min and formation of Au layer over IONP via using hydroxylamine hydrochloride as reducing agent. The resultant theranostic mGNP were utilized for diagnosis by MRI and photothermal treatment of colon cancer.

2.4. Brust–Schiffirin Method

The Brust–Schiffirin method is a widely used method for the preparation of thiol functionalized highly stable metallic nanoparticles with solubility in organic solvents, where, metal precursors are reduced by NaBH_4 in presence of alkanethiol in a two-phase system i.e., water and toluene. The Brust–Schiffirin method for GNP involves HAuCl_4 (Au^{3+}) phase transfer to the organic phase from the aqueous phase with the help of phase transfer catalyst, followed by reduction of Au^{3+} to Au^{1+} and Au^0 using dodecanethiol and NaBH_4 , respectively [74,75]. This method is basically a chemical reduction with a two-step process performed at room temperature and gives very stable and small magnetic-plasmonic nanoparticles but with a complicated process [37].

In a study by Park et al. [59] this method with thermally activated process protocols was utilized with modifications to produce Fe core and Au shell mGNP with a 2 nm size of GNP for bio-separation and interfacial bioactivity applications. They prepared oleic acid-coated IONP by heating a mixture of $\text{Fe}(\text{CO})_5$ and oleic acid in phenyl ether at high temperatures with continuous stirring followed by precipitation of nanoparticles with ethanol. Finally, GNP were synthesized by Brust–Schiffirin method and coated over oleic acid-coated IONP producing mGNP with 5 to 100 nm size and high monodispersity. A thermal-activated study was conducted on MNP and GNP indicating growth of GNP over MNP (Table 1). The–Brust Schiffirin method was also used by several researchers to produce magnetic-plasmonic nanoparticles with the magnetic core being based on nickel ferrite [7] or Co [76].

3. Biological Applications of mGNP

The mGNP are multifunctional nanohybrid systems with magnetic and plasmonic properties that promote their use in biomedical applications as mentioned in Table 2. In this review, we will discuss the most recent biological applications of mGNP including drug and gene delivery, bioimaging, and biosensing. The biomedical applications of mGNP in neuro-regeneration, neuro-degenerative and arthritic disorders, based on the latest research works, will also be discussed in this review.

Table 2. Applications of magnetic gold nanoparticles in biological sciences.

Magnetic Gold Nanoparticles	Biological Applications	References
$\text{Au}/\text{Fe}_3\text{O}_4/\text{PVA}^1$	Multi-stimuli mGNP ² for synergistic and targeted DXL ³ delivery for MCF-7 human breast cancer cells	[77]
PBMA-NH ₂ ⁴ grafted thiolated sodium alginate	Paclitaxel loaded hydrophobically modified theranostic mGNP for PLC/PRF/5 human hepatocellular carcinoma cells	[78]
mGNP-DOX ⁵	Theranostic mGNP showing efficacy against Ehrlich carcinoma tumor model in mice	[23]
Fe–Au alloy mGNP	Serves as targeted drug carrier for delivery of MTX ⁶ to hepatocellular carcinoma cells (HepG2) with hyperthermia controlled MTX release	[79]
HA ⁷ -PEI ⁸ -Au/ Fe_3O_4	Effectively suppress growth of prostate cancer (PC3) cells in vitro by magnetically targeted delivery of ADAM10 siRNA loaded HA-PEI-Au/ Fe_3O_4	[25]

Table 2. Cont.

Magnetic Gold Nanoparticles	Biological Applications	References
Au/PPy ⁹ @Fe ₃ O ₄	Multi-purpose mGNP for magnetically guided photothermal therapy and contrast agent for MR ¹⁰ and CT ¹¹ imaging	[16]
Au-Fe Janus mGNP	Contrast agents for multimodal imaging by MR, CT, and photoacoustic imaging to visualize cellular uptake	[57]
Antigen labeled Fe ₃ O ₄ -Au	Used as immunosensors to detect digoxin in range from 0.5 to 5 ng mL ⁻¹ in biological samples	[80]
SMS ¹² -Au-SPION ¹³	Targeted strategy for Parkinson's disease where SMS promoted intracellular uptake of Au-SPION to delay blockage of L-type voltage-gated Ca ²⁺ channel in midbrain neurons	[81]
NGF ¹⁴ functionalized SPION-Au	Magnetically driven cellular uptake of mGNP was enhanced onto adrenal pheochromocytoma (PC-12) cells due to NGF functionalization in addition to NGF induced neurite length elongation	[82]
PLGA ¹⁵ /Au/Fe/Au-RGD ¹⁶	MTX loaded PLGA/Au/Fe/Au-RGD hybrid nanoparticles are magnetically guided chemo-photothermal carriers used as anti-inflammatory agents for RA ¹⁷ and enable in vivo T2-MRI	[36]

PVA¹: polyvinyl alcohol; mGNP²: magnetic gold nanoparticles; DXL³: docetaxel; PBMA-NH₂⁴: amine-terminated poly butyl methacrylate; DOX⁵: doxorubicin; MTX⁶: methotrexate; HA⁷: hyaluronic acid; PEI⁸: polyethyleneimine; PPy⁹: polypyrrole; MR¹⁰: magnetic resonance; CT¹¹: computed tomography; SMS¹²: static magnetic field stimulation; SPION¹³: superparamagnetic iron oxide nanoparticles; NGF¹⁴: nerve growth factor; PLGA¹⁵: poly(lactic-co-glycolic acid); RGD¹⁶: arginine-glycine-aspartic acid; RA¹⁷: rheumatoid arthritis.

3.1. mGNP as Drug and Gene Delivery Carriers

The mGNP have been used successfully as carriers for drug and gene delivery applications. Drug delivery systems based on mGNP can have different mechanisms for drug release, for example, Taheri-Ledari et al. [77] loaded docetaxel into polyvinyl alcohol (PVA) layer over mGNP and utilized it for the treatment of human breast cancer tumors. The temperature-triggered drug release phenomenon occurred by these magneto-plasmonic nanoparticles in normal and cancerous cells as shown in in vitro studies. Magnetically targeted mGNP indicated drug release due to acidic pH in cancerous cells. Therefore, the combination of pH-controlled and temperature-triggered drug release with magnetically targeted delivery docetaxel makes the mGNP a potential multifunctional drug delivery system. Arora et al. [78] produced paclitaxel-loaded mGNP with a higher encapsulation efficiency of drug and efficacy against human hepatocellular carcinoma cells.

In a study, mGNP were coated with thiolated PEG followed by the attachment of anticancer DOX through electrostatic interactions. The antitumor effects were obtained by releasing DOX as released in a controlled manner at the tumor site using magnetic targeting and inducing photothermal therapy via using NIR laser radiations. In addition to antitumor effects, the theranostics mGNP were also utilized as contrast agents for MRI in concerned in vivo models. The study successfully concluded that mGNP can be effectively utilized as MRI contrast agents for guided chemo-photothermal synergistic therapy [23].

In another study [79], mGNP were employed to deliver methotrexate (MTX) to liver carcinoma (HepG2) cells. In this study, MTX was covalently attached to mGNP by 2-aminoethanethiol grafting method. They applied external magnetic fields to the nanohybrid system indicating hyperthermia-mediated controlled drug release in an incremental manner. In a study by Elbially et al. [31] mGNP were utilized to reduce the toxicities of DOX in cancerous patients by using a magnetically targeted phenomenon.

For instance, PEI capped mGNP [25] can be used for effective biomedical applications of gene and siRNA. Hyaluronic acid was used to target prostate cancer (PC) cells. The prepared HA-PEI-Au/Fe₃O₄ NPs delivered ADAM10 siRNA effectively to suppress the PC3 cell growth and appeared to be biocompatible for intracellular delivery of siRNA. A similar study carried out by Chen et al. [83] used AU-MNPs to deliver Notch3 siRNA constructed by VEGF RNA aptamer chimera. The obtained complex exhibited much

higher silencing efficiency against Notch3 gene in ovarian cancer cells and improved the antitumor effects.

In another study [73], SPIO-Au mGNP were developed to target MCF-7 (MUC-1 aptamer positive) and CHO (MUC-1 aptamer negative) cancer cell lines. Results showed that the developed formulation had more cellular uptake for MCF-7 cells as compared to CHO cancer cells.

3.2. mGNP as Imaging Agents

Multifunctional mGNP have been successfully employed for theranostic applications for simultaneous therapy and imaging. Most mGNP show multi-modal imaging phenomenon increasing the number of diagnostic tools with convenience and effectiveness. Multifunctional mGNP as a theranostic platform were developed by Feng et al. [16] A triple functional agent based on GNR and IONP into PPy. Such an agent (Au/PPy@Fe₃O₄) not only exhibited high contrast for MRI and CT imaging but also showed cytotoxicity by photothermal effects.

For Fe₃O₄@SiO₂-PrNH₂@Au, APTES was used to functionalize mGNP that were used as MRI and CT scan contrast agents in human hepatocellular carcinoma [84]. Sodium citrate-based Fe₃O₄@Au mGNP [2] were developed as MRI and CT scan contrast agents by Mohajer et al. Fe/Fe₃O₄ PrNH₂@Au were synthesized as bifunctional magnetic plasmonic nanostructures for applications in MRI and magneto-optical thermal therapies [85]. Reguera et al. [57] also developed Fe₂O₃@Au Janus magnetic-plasmonic nanoparticles for photoacoustic imaging, MRI, and CT scan contrast agents.

3.3. Advantages of Au Coating over Magnetic NPs for MRI

During the last decades, the Au coating has been suggested for contrast enhancement over magnetic nanoparticles for MRI. The iron coating as a contrast agent over Fe NPs imparts attractive features to the multi-layered NPs for MRI exhibiting up to 200 times improved field relativity ($r_1 = 3.0 \text{ mM}^{-1} \text{ s}^{-1}$ to $585 \text{ mM}^{-1} \text{ s}^{-1}$). Scientists reported that AuNPs coating over Fe NPs can be used to attach to hundreds of ligands and to carry gadolinium chelates to further enhance contrast capabilities with improved anti-tumor targeting, imaging, and immunotherapy [86].

3.4. mGNP as Biosensors

The mGNP can be potentially developed for use in the diagnosis of various diseases and in vivo detection of drugs utilized for the treatment of diseases. For instance, a lateral flow immunochromatographic assay system was developed for the detection of immunoglobulin M (IgM) related to TORCH infections (T-toxoplasmosis, O-other agents, R-rubella, C-cytomegalovirus, and H-herpes simplex virus) based on mGNP [87]. IgM antibodies to four types of pathogens were detected using the constructed device and displayed higher sensitivity. The mGNP showed 100% sensitivity and 100% selectivity in 41 seropositive and 121 seronegative samples. Another study against HBV was conducted by Mashhadizadeh et al. [88] who prepared an mGNP modified with a carbon paste electrode for immobilization of thiol modified HBV probe DNA and determined its trace amount. The proposed DNA biosensor could measure HBV DNA concentration with a low detection limit of $3.1 (\pm 0.1) \times 10^{-13} \text{ M}$, much lower than the detection limit reported with GNP or MNP alone. This work was successfully utilized for sensitive detection of HBV target in urine and blood plasma.

Besides application in the treatment of cardiovascular diseases, mGNP have also been utilized in the detection of cardiac markers and cardiac drugs. Gold-coated MNPs [80] were used as electrochemical immunosensor for digoxin (Fe₃O₄-Au-NPs). The developed immunosensor was able to detect digoxin with a detection limit of 0.05 ng mL^{-1} . The study concluded that the proposed method had acceptable reproducibility, stability, and reliability upon detection of digoxin in serum samples.

3.5. mGNP in Neuro-Regeneration and Neuro-Degenerative Disorders

Due to the slow rate of axonal regeneration [82], neuro-regeneration is one of the most significant challenges in neuroscience. Extensive studies employed in the last decade were targeted at increasing the speed of neuron recovery. Many efforts have been made to develop molecules [89], proteins [90], biomaterials [91], and growth factors [92] that possess the ability for axonal regrowth. The pharmacological effects of such agents require them to be released continuously intracellularly [93] and require easy transport through the blood–brain barrier (BBB) [82]. Although MNP have been demonstrated as effective carriers for neuro-regenerative agents, the direct use of uncoated MNP possess challenges of instability in the neuronal environment, aggregation [82], and cellular toxicity [94]. Hence, they have been protected by coating materials including Au. mGNP have been used as a carrier for efficiently transporting neuro-regenerative agents across BBB to enhance the half-life and efficiency in promoting neuronal growth. Recently, Yuan et al. employed the use of MNP coated with Au for precise control of neuro-regeneration towards PC-12 cells. They developed Au-coated MNP functionalized with NGF (nerve growth factor) by dynamic magnetic field technique. Cells treated with NGF-IO-Au NPs were studied for cellular uptake and cell viability. The results confirmed that dynamic magnetic field performed better in neuro-regeneration than static ones. Experimental data was also confirmed by cytoskeleton force model to predict the neurite elongation and orientation [82,95].

Similarly, other research conducted more recently by Yuan et al. [93], reported the development of mGNP conjugated with porous coordination cages for controlled drug release in neuro-regeneration in PC-12 cells. The pyrene-PEG-SH bridge enabled functionalization of mGNP with PCC-3 and resulted in higher interaction with PC-12 neuron-like cells. With negligible toxicities, IO-Au-RhB-PCC-2(3) nanocarrier exhibited effective drug loading of retinoic acid (RA) and controlled release using low-intensity LED lights.

Chen et al. [96] reported the development of PEG-coated mGNP modified with insulin targeted to brain cells. They found out that the concentration of developed formulation using the physiologically based pharmacokinetic model, advection-diffusion equation, and COMSOL multiphysics. The results showed good permeability, in vivo bio-distribution, and bioavailability of 24.47% which further improved bioavailability by 3.91% under SMF.

Most recently, in 2022, mGNP were studied for modulating neuronal excitability and outgrowth [81]. Static magnetic field stimulation gold-coated MNP were assessed for effects on brain physiology and it was found that SMS enhanced brain uptake of mGNP, delayed blockade, reduced frequency, and decreased Ca^{2+} fluxes amplitude at L-type voltage-gated Ca^{2+} channel (VCGG). Thus, by modulating VGCC, SMS-IO-Au mGNP can be used for neuronal outgrowth and as a drug delivery strategy to treat Parkinson's disease.

3.6. mGNP in Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease with joint inflammation resulting in cartilage and bone damage leading to systemic complications. It is important to assess the long-term effectiveness and safety of RA therapies. Nanotechnology-based interventions and strategies help overcome challenges associated with conventional medicines such as low solubility, permeability, penetrability, poor bioavailability, systemic toxicity, poor ligand-target interaction producing sub-therapeutic response [97–99].

Recently, a published study served as proof for use of mGNP as an attractive alternative for future treatment of rheumatic diseases. The study was aimed at the use of mGNP as magnetically targeted to the arthritic articulation of collagen-induced arthritis (CIA) [100]. The mGNP led to significant clinical improvements i.e., suppresses joint edema, infiltration by leukocytes, inflammation as well as TNF- α (tissue necrosis factor- α) and IL- β (interleukin- β) expression in synovium accompanied by lack in toxicity. Another study [36] carried out for the chemo-photothermal treatment of RA was conducted on MTX-loaded PLGA/Au-/Fe mGNP followed by conjugation of arginine-glycine-aspartic acid (RGD) with a second layer of Au being applied on Fe layer to prepare MTX loaded PLGA/Au-/Fe/Au-RGD. Upon application of magnetic field, local heat generated at in-

flammation region and MTX release from mGNP is accelerated. They also enable in vivo T2-MRI. Besides that, they when combined with NIR irradiation and external magnetic field, mGNP retention can be enhanced.

3.7. Gold-Magnetic Nanoparticles for Enhanced Therapeutic Effects

Many tumors express heparanase as the tumor-related antigen. Recently, a group of scientists developed heparanase targeting Au-Fe nanoparticle probes (30 nm). The Au-Fe NPs worked as a contrast agent and were functionalized with heparanase monoclonal antibodies to target cancer cells. This antitumor immunotherapy approach using 3.0 T MRI showed the effectiveness of these nanoprobe for identifying metastasis by observing reduced T2WI signals during magnetic resonance imaging (MRI). The heparanase functionalization on the surface of Au-Fe NPs showed enhanced antitumor targeting to reduce off-target toxic effects [101].

4. Conclusions and Future Perspectives

In this review, we have discussed the latest synthetic techniques and biomedical applications of mGNP majorly developed over the previous six years. Multifunctional mGNP have gained great importance in modern research due to their multifunctional capabilities. Different techniques have been utilized to effectively formulate mGNP for biomedical applications including coprecipitation, thermal decomposition, microemulsion, and Brust–Schiffrin. Their morphology and size can be tuned by various synthetic techniques with a wide variety of surface functionalization by using different materials as discussed in our review. Furthermore, the unique features of hybrid magnetic-plasmonic nanoparticles based on Fe core and Au shell demonstrate them as the most promising systems for drug and gene delivery, bioimaging, biosensing, and most importantly for neuro-regeneration, neuro-degenerative and arthritic disorders. In future, the utilization of mGNP as targeted carriers for insulin, antiarthritic drugs, and antitumor for solid cancers including glioblastoma will be of great importance. Moreover, gold has prominent anti-inflammatory effects which can be used for synergistic purposes in the treatment of inflammatory conditions. Furthermore, mGNP further needs to be investigated to provide proof of concept to establish them for preclinical and clinical studies. The biodistribution and pharmacokinetics of mGNP are crucial to be investigated first in preclinical studies followed by clinical studies. Most importantly the toxicity studies of mGNP needs to be further investigated and understood.

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