Review article

Rise of Gold Nanoparticles as Carriers of Therapeutic Agents

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Abstract

Nanoparticles are typically nanoscopic materials with at least one of the dimensions below 100 nm having diverse applications in many industries. The latest developments in nanotechnology provide a wide range of methods for studying and monitoring various medical and biological processes at the nanoscale. Nanoparticles can help diagnose and treat diseases, such as cancer, by carrying drugs directly to cancer cells. They can also be used to detect disease biomarkers in the body, helping to provide early diagnosis. It is plausible that nanoparticles could be used in theranostic applications and targeted drug delivery. This could significantly improve patient outcomes and reduce the amount of time, effort, and money needed to diagnose and treat diseases. It could also reduce the side effects of treatments, providing more precise and effective treatments. Nanoparticles for biomedical applications include polymeric and metal nanoparticles; liposomes and micelles; dendrimers and quantum dots; etc. Among the nanoparticles, gold nanoparticles (GNPs) have emerged as a promising platform for drug delivery applications. GNPs are highly advantageous for drug delivery applications due to their excellent biocompatibility, stability, and tunable physical and chemical properties. The present review provides an in-depth discussion of the various approaches to GNPs synthesis and drug delivery applications.

Keywords: Bio-degradable; gold nanoparticles; drug delivery; drug targeting; cancer therapy; gene delivery; protein delivery, Vaccine delivery; siRNA delivery.

1. Introduction

Researchers across the world have offered viable solutions for the optimal delivery of challenging therapeutic agents so as to achieve the best clinical outcomes in diverse disease conditions. In this scenario, nanotechnology-driven technology platforms stood very effective for drug delivery and other biomedical applications.[1–8] One of the first metals discovered, gold, has had a long and illustrious study and implementation chronology. Arab, Chinese, and even Indian researchers attempted to create colloidal gold as early as the fifth and fourth century BC, according to early treatises on the subject. European alchemist laboratories investigated and used colloidal gold during the Middle Ages for the treatment of various ailments including syphilis, leprosy, plague, epilepsy, diarrhea, and mental disorders. In the last few years, nanoparticles based on gold chemistry have drawn considerable research and practical attention. They are versatile biological agents that can be used in a variety of applications, including very sensitive analytical assessments, the creation of ablation heat and radiation, and the transfer of drugs and genes.[9–11] In order to interact with cells or biomolecules in biomedical applications, gold nanoparticles (GNPs) must be externally functionalized. A high surface area to volume ratio, the ability to be modified with ligands containing functional groups such as thiols, phosphines, and amines, and the ability to bind to gold surfaces are some of the unique properties of the GNP that have been developed.[12–14] Additional moieties, including proteins, oligonucleotides, and antibodies, can be attached to the ligands using these functional groups. Compared to GNPs, silver nanoparticles can be more reactive and prone to oxidation, potentially limiting their stability and performance over time.[15]

While silver nanoparticles have antimicrobial properties, excessive release of silver ions from the nanoparticles can raise toxicity concerns, particularly in biological and environmental contexts. GNPs are favored for their biocompatibility, stability, and functionalization capabil-

ities, making them suitable for biomedical and targeted delivery applications. These nanoparticles can be easily functionalized with biomolecules, such as antibodies and peptides, for targeted drug delivery and molecular interactions. The stability of GNPs ensures that these functionalized coatings remain intact, allowing for precise and controlled interactions with biological systems. GNPs exhibit unique catalytic properties, particularly in selective oxidation reactions. While silver nanoparticles also possess catalytic activity, the selectivity and efficiency of GNPs make them preferable for certain catalytic applications. These unique physical and chemical properties of GNPs allow for various applications. Recent research suggests that GNPs can be used as efficient medication carriers since they can enter organelles in addition to infiltrating blood vessels to reach the tumor's site.[14,16] GNPs can also release their payload at the target spot in response to an internal or external stimulus. Our review makes an effort to present a thorough overview of the most promising uses of GNPs in contemporary scientific studies, while also taking into account the amount of data produced and the rate at which it is updated.

2. Synthesis of GNPs

Synthesis of GNPs follows the same "Top-Down" and "Bottom-Up" methodologies as other inorganic and metal nanoparticle synthesis. Synthesizing GNPs from bulk material and breaking them down into nanoparticles in a variety of ways is the top-down approach. On the other hand, nanoparticles are synthesized using the bottom-up method, which begins at the atomic level. Laser ablation, ion sputtering, ultraviolet, and infrared irradiation, and aerosol technology are all examples of top-down approaches to synthesis, while the reduction of gold III ions (Au^{3+}) is an example of a bottom-up strategy.[17] The synthesis strategies are discussed in the following section. (Figure 1).

Figure 1: Strategies for synthesis of gold nanoparticles.

2. 1. Citrate Reduction (Turkevich Method)

Most methods of synthesizing GNPs require reducing an aqueous gold solution to gold nanoparticles (in fact, elemental gold) using specific reducing chemicals, followed by stabilizing the newly created nanoparticles. In the second stage of stabilization, sulfonated and non-sulfoned sulphur compounds, polymers, and surfactants are all utilized to prevent GNPs from aggregating.[18,19]

Recently few green approaches have also been introduced for the fabrication process. Green chemistry refers to chemical synthesis techniques that are safe for the environment and do not harm live organisms.[18] There is evidence that the biomaterial Egg shell membrane (ESM) can be used to effectively produce GNPs via green biosynthesis.[19]

The most popular technique for generating GNPs is the Turkevich reductive approach.[20] In this process, sodium citrate ($Na_3C_6H_5O_7$) and chloroauric acid ($HAuCl_4$) react to produce colloidal gold.[21] The reduction of citrate was modified by the group of scientists led by Frens to get GNPs with sizes ranging from 2 to 330 nanometers.[22,23] The particle size of the GNPs fabricated via the Turkevich method is grossly affected by various parameters like the molar ratio of the reactants, production batch size, reaction temperature, pH, and the order of addition of reactants.[20]

2. 2. Brust-Schiffrin Strategy

GNPs with lower dispersion values may be produced via Brust Schiffirin reaction.[21] The procedure involves producing GNPs from chloroauric acid ($HAuCl_4$) in a non-aqueous solution by reducing Au(III) with sodium borohydride and tetraoctyl ammonium bromide.[22] The addition of the reducing agent causes the organic phase to change color from orange to dark brown. This demonstrates the existence of GNPs.

The Brust-Schiffrin strategy has been widely applied in the preparation of GNPs, and it has played a significant role in the advancement of nanotechnology.[22] GNPs have unique properties due to their small size and high surface area-to-volume ratio, making them attractive for various applications in catalysis, electronics, medicine, and more. Let's explore how the Brust-Schiffrin strategy is helpful in the preparation of gold nanoparticles:

Core Formation: The first step in the Brust-Schiffrin method involves functional group transformations.[24] In the context of GNPs synthesis, this step focuses on creating a gold core with the desired size. Usually, a gold precursor, such as gold chloride ($AuCl_3$), is reduced using a suitable reducing agent. For example, sodium borohydride ($NaBH_4$) is a common reducing agent in this context. The reduction reaction leads to the formation of tiny gold clusters or nuclei.[24]

Surfactant-Mediated Growth: The Brust-Schiffrin strategy relies on surfactants, which are molecules that can stabilize and control the growth of nanoparticles. In the case of GNPs, ligands like alkanethiols or alkylamines are commonly used as surfactants.[24] These surfactants bind to

the GNPs' surfaces, preventing them from agglomerating and stabilizing their size and shape.

Convergent Assembly: After obtaining the gold nuclei, the next step is the convergent assembly, where the small gold clusters are brought together to grow into larger nanoparticles.[24] In this process, the surfactants play a crucial role. They act as linkers, guiding the gold clusters toward each other, resulting in the formation of larger nanoparticles.

Protecting Group Strategy: In the context of GNPs synthesis, the protecting group strategy is not directly involved, as it is typically applied in multi-step organic synthesis.[22] However, the surfactants mentioned earlier can be considered akin to protecting groups, as they prevent the gold clusters from coalescing and facilitate controlled growth.

The Brust-Schiffrin strategy in GNPs synthesis has many advantages. The modular nature of the strategy allows for the synthesis of GNPs with different sizes and surface functionalities. By controlling the starting materials, surfactants, and reaction conditions, researchers can fine-tune the properties of the nanoparticles for specific applications. The strategy enables precise control over the size of the resulting nanoparticles. The initial size of the gold nuclei can be adjusted by varying the amount of reducing agent and reaction time. The surfactants further regulate the growth of the nanoparticles, ensuring a uniform and controlled size distribution. Furthermore, the use of surfactants in the Brust-Schiffrin method promotes the formation of monodisperse nanoparticles, meaning that the particles have a narrow size distribution. This is crucial for many applications where consistent particle size is desirable. The Brust-Schiffrin strategy often yields a high percentage of monodisperse nanoparticles, contributing to its efficiency and cost-effectiveness. Hence, the Brust-Schiffrin strategy has proven to be a valuable approach for the preparation of GNPs. It offers control over the size, shape, and surface properties of the nanoparticles, making them suitable for various applications in nanotechnology and beyond. The ability to synthesize GNPs with precise characteristics has opened up new possibilities in fields such as catalysis, sensing, imaging, and targeted drug delivery.[22]

2. 3. Electrochemical Strategy

GNPs can be created electrochemically in a two-electrode cell with the cathode reduced and the anode oxidized. Reetz and Helbig (1994) introduced the concept of creating nanoparticles via electrochemical techniques.[23] This method has been considered preferable to other ways of nanoparticle synthesis because of its low processing temperature, low cost, high quality, simple equipment, and ease of process management.[25] The electrochemical synthesis method was used to create GNPs on the surface of multi-walled carbon nanotubes with glassy carbon electrodes. [26] Tetra dodecyl ammonium bromide as a surfactant stabilizer has been used to stabilize the size-controlled GNPs fabricated via electrochemical synthesis.[27]

In an electrochemical cell, the cathode is immersed in an electrolyte solution containing gold ions, such as HAuCl4. An external power source, such as a battery or a potentiostat, is connected to the cathode and anode, creating an electric potential between the two electrodes. At the cathode, gold ions (Au^{3+}) from the electrolyte solution gain electrons and undergo reduction, resulting in the formation of elemental gold (Au^0) nanoparticles on or near the cathode surface.[28] This reduction process is the key step in the electrochemical synthesis of GNPs. Simultaneously, at the anode, a counterreaction occurs to balance the reduction process at the cathode. In the case of an aqueous electrolyte, water molecules may be oxidized to produce oxygen gas and protons (H^+). The size and shape of the synthesized GNPs can be controlled by adjusting the experimental parameters, such as the applied potential, the concentration of gold ions in the electrolyte, and the reaction time.

Electrochemical methods offer several advantages for GNPs synthesis, including precise control over the size and shape of the nanoparticles and the ability to perform the synthesis in a more environmentally friendly manner. Additionally, this approach can be easily scaled up for large-scale production of GNPs.

Role of Electrodes: The cathode is the electrode where reduction reactions occur. In the case of GNPs synthesis, the cathode serves as the site for the reduction of gold ions (Au3+) to elemental gold (Au^0) that forms the nanoparticles.[28] Electrons from an external power source are supplied to the cathode, promoting the reduction reaction. Typically, the cathode is made of a conductive material, such as a metal or a conductive glass substrate. On the other hand, the anode is the electrode where oxidation reactions occur. During the electrochemical synthesis of GNPs, the anode is typically made of an inert material that does not participate in chemical reactions. Its primary function is to provide a site for the oxidation of a counter-reaction that balances the reduction occurring at the cathode. For example, in an aqueous solution, water molecules can be oxidized to produce oxygen gas and protons (H+), thus balancing the reduction of gold ions at the cathode.[28,29]

2. 4. Seeding Growth Strategy

Since several years ago, attention has been focused on the large-scale synthesis of GNPs in order to meet the huge demand for these materials. Using Oleyl amine as a reducing and stabilizing agent, GNPs with an average diameter of 9 nm were created in toluene.[30] These GNPs operate as seeds for subsequent growth reactions in which the identical precursors are progressively added to the reaction vessel (Figure 2). Tan et al (2015) synthesized stable GNPs (size ranging 7–30 nm) using a seeding growth

technique.[31] The dispersion is highly disseminated and consistent with the particle size, as seen by the Transmission electron microscopy (TEM) images and optical absorption spectra of the GNPs.

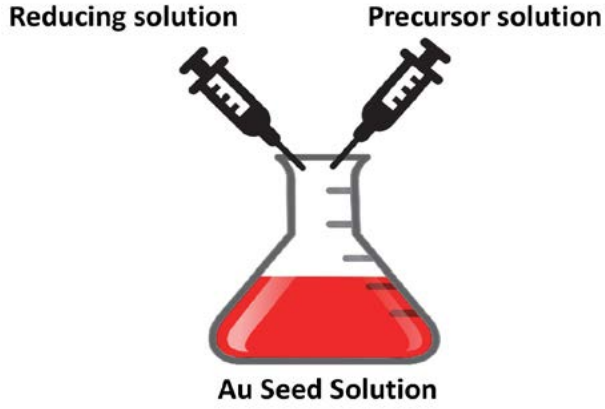

Figure 2. Synthesis of gold nanoparticle via seeding growth strategy.

In this approach, the synthesis is initiated using preformed seed nanoparticles with specific crystal facets. The seed nanoparticles act as nuclei for further crystal growth, guiding the formation of anisotropic shapes like gold nanorods, nanostars, nanocubes, and nanoplates.[32]

Compared to other synthesis methods, the seeding growth strategy offers several advantages. One notable advantage is the ability to precisely control the size and shape of the nanoparticles by adjusting the seed size and growth conditions. This level of control is particularly important in nanotechnology and nanoscience applications where specific shapes are required to tailor the nanoparticles' properties for different uses.

Once the seed nanoparticles are synthesized, they can be used as templates for the large-scale production of anisotropic GNPs.[32] The ability to synthesize a large number of nanoparticles with consistent shapes and sizes is advantageous for industrial applications, where reproducibility and scalability are critical factors.

Furthermore, the seeding growth method enables the synthesis of complex nanoparticle shapes that might be challenging to achieve using other techniques. For example, gold nanostars, with their unique sharp protrusions, have specific plasmonic properties that make them attractive for biomedical imaging and therapeutic applications.

In research and industrial settings, large-scale synthesis of GNPs with controlled shapes is essential for various applications. For instance, in the field of catalysis, well-defined nanoparticle shapes can enhance catalytic activity and selectivity. In biomedicine, the size and shape of GNPs play a crucial role in their interactions with biological systems, influencing their behavior as drug carriers, imaging agents, or therapeutics.

To demonstrate the significance of the seeding growth strategy, researchers often specify the number of nanoparticles synthesized. The ability to produce grams or even kilograms of anisotropic GNPs with reproducible shapes and properties showcases the suitability of this method for practical applications.[33]

Overall, the seeding growth strategy for GNPs synthesis is a versatile and efficient method for large-scale production of nanoparticles with tunable shapes. Its potential for creating well-defined anisotropic shapes makes it an attractive choice for various technological and biomedical applications. Researchers continue to refine and optimize this method to meet the increasing demand for tailored nanoparticles with precise properties and functionalities.

2. 5. Photochemical Strategy

Due to the improved spatial and temporal control that these technologies provide, photochemical approaches have attracted a lot of attention in the production of metallic NPs.[34] A typical experiment involves irradiation of visible or ultraviolet (UV) light on solutions containing the metal precursors. Photochemical routes in nanotechnology are preferable to other approaches, such as chemical approaches, because they avoid the use of toxic or harmful compounds, do not require expensive equipment or highly skilled personnel, and, most importantly, can be completed at ambient conditions, such as room temperature and atmospheric pressure.[34–36]

The photochemical method for GNPs synthesis is a versatile and widely used approach that involves the use of light energy to drive the reduction of gold ions and the subsequent formation of GNPs.[37] This method typically employs a photosensitive compound, known as a photosensitizer or a stabilizer, which absorbs light and transfers the energy to the gold ions, initiating the reduction process (Figure 3).

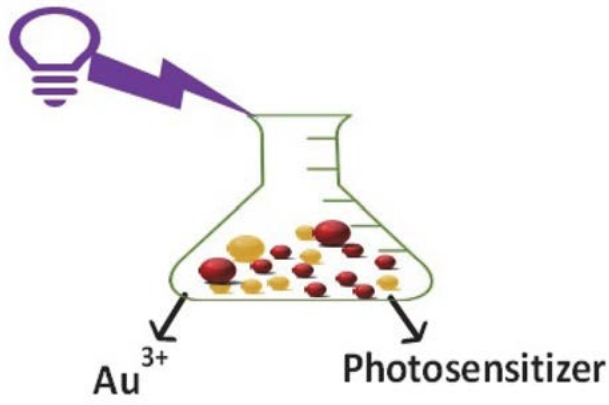

Figure 3. Photochemical synthesis of gold nanoparticles.

The key steps involved in the photochemical synthesis of GNPs are as follows:

Photosensitizer Selection: The choice of a suitable photosensitizer is crucial in this method. Photosensitizers are molecules that have the ability to absorb light energy and undergo a photochemical reaction. These molecules should be compatible with the gold precursor solution and facilitate the reduction of gold ions when excited by light.

Light Irradiation: The photosensitizer-bound gold precursor solution is exposed to light of a specific wavelength that matches the absorption spectrum of the photosensitizer.[37] This light irradiation leads to the activation of the photosensitizer, resulting in the generation of reactive species or electrons with high reducing potential.

Gold Ion Reduction: The activated photosensitizer transfers the energy to the gold ions present in the solution. The excited gold ions then undergo reduction to form GNPs. The reaction typically involves the transfer of electrons from the excited state of the photosensitizer to the gold ions, leading to the conversion of Au3+ (gold ions) to Au0 (elemental gold).

Nanoparticle Stabilization: As the reduction process proceeds, the formed GNPs are often stabilized and capped by the surrounding stabilizing agents or the photosensitizer itself. These stabilizing agents prevent the nanoparticles from aggregating and aid in controlling the size and shape of the nanoparticles.

The photochemical method offers several advantages for GNPs synthesis. One of the significant advantages is the ease of control over the size and shape of the nanoparticles. By adjusting the light intensity, duration of light exposure, and concentration of the photosensitizer, researchers can tune the synthesis conditions to obtain GNPs with specific properties tailored for different applications.[37]

Moreover, the photochemical method is relatively fast, allowing for rapid nanoparticle synthesis. It also offers the potential for spatial control over nanoparticle formation, enabling localized synthesis in specific regions using patterned light sources or photomasks.

Researchers have explored various photosensitizers for GNPs synthesis, including organic dyes, metal complexes, and semiconductor nanomaterials like quantum dots.[38] Each type of photosensitizer has its specific advantages and can lead to different nanoparticle properties.

The photochemical method has found applications in diverse fields, including nanomedicine, catalysis, and sensing. The ability to use light as a trigger for nanoparticle synthesis offers unique opportunities for on-demand and controlled nanoparticle production, making it a promising technique for future advancements in nanotechnology and nanoscience.

It is worth noting that while the photochemical method is powerful, the choice of the photosensitizer, light source, and reaction conditions should be carefully optimized to achieve desired nanoparticle properties and prevent unwanted side reactions.[39] Therefore, researchers continue to explore and develop this method, advancing the synthesis of GNPs for a wide range of applications.

2. 6. Ultrasound-aided Synthesis of GNP

Sonochemistry, a rapidly growing area of chemistry that is focused on the ultrasonic (US) effect and acoustic cavitation, has grown significantly during the past several decades. In a liquid media, US-induced pressure variations cause bubbles to develop, expand, and implosively collapse. There is a significant buildup of energy inside the bubble as a result of the bubble collapsing. The tiny bubbles may potentially deagglomerate nanoparticles, break larger particles into smaller ones, or collapse at the surface of a solid substrate and activate it. Researchers across the world tried this technology for the fabrication of GNPs.[40–44] GNPs synthesized with ultrasound have been shown to have a smaller particle size (13.65 nm vs 16.80 nm), and greater yield than their non-ultrasound counterparts.[44] In another effort, Chen et al (2011) reported a single-step fabrication of spherical and plate-shaped GNPs using the ultrasonication method.[43]

Significance of the Cavitation Process

In the ultrasound-aided synthesis of GNPs, the phenomenon of cavitation plays a crucial role in enhancing the nanoparticle formation process. Cavitation is a physical process that occurs when ultrasound waves pass through a liquid medium, leading to the formation, growth, and implosion of microscopic bubbles.

During the ultrasound-assisted synthesis of GNPs, the gold precursor solution is exposed to ultrasonic waves.[45,46] These waves create alternating high-pressure and low-pressure regions in the liquid medium. When the pressure in the low-pressure regions drops below the vapor pressure of the liquid, small gas bubbles are formed. These bubbles continue to grow during the low-pressure phase of the ultrasound wave.

As the ultrasound wave progresses to its high-pressure phase, the surrounding pressure rapidly increases. The rapid change in pressure causes the bubbles to violently collapse or implode. This implosion generates intense localized energy, resulting in high temperatures and pressures in the vicinity of the collapsing bubbles. These extreme conditions trigger the reduction of gold ions present in the solution, leading to the formation of GNPs.[45]

The cavitation process during ultrasound-aided GNP synthesis enhances the kinetics of the reduction reaction and promotes the formation of smaller and more uniform nanoparticles. The violent collapse of bubbles generates hotspots with high energy, which facilitate the reduction of gold ions to elemental gold more efficiently. Additionally, the turbulence created by cavitation helps in mixing and homogenizing the reaction mixture, leading to better control over nanoparticle size and shape.

Furthermore, the cavitation phenomenon can aid in the reduction of polydispersity, resulting in a narrower size distribution of the synthesized GNPs.[47] The rapid and localized nature of the cavitation process also enables the

synthesis of GNPs with shorter reaction times compared to conventional methods.

The ultrasound-aided synthesis of GNPs through cavitation has found applications in various fields, including catalysis, biomedical imaging, and drug delivery. The ability to control nanoparticle size and morphology with enhanced efficiency makes this approach valuable for tailoring GNPs for specific applications.

However, it is important to carefully optimize the ultrasound parameters, such as frequency, power, and exposure time, to avoid undesired effects like overheating or the formation of non-uniform nanoparticles.[45,47,48] Researchers continue to explore and refine ultrasound-aided synthesis methods to harness the benefits of cavitation for precise and controlled nanoparticle synthesis.

2. 7. Laser Ablation Synthesis of GNPs

Pulsed lasers are utilized nowadays to treat materials and advance numerous chemical reactions. When a target submerged in a liquid is exposed to pulsed laser energy, the target and solution form a dispersion after cavitation bubbles, shock waves, and secondary photons are produced.

By using laser ablation, precise and repeatable results have been achieved in terms of both form and size. Sahebi et al (2019) reported the fabrication of colloidal GNPs using pulsed laser ablation reduction of aqueous gold precursor.[49] By applying the laser ablation approach with a low-power neodymium yttrium aluminum garnet (Nd:YAG) laser at the fundamental wavelength, high-purity GNPs have been effectively produced by Khumaeni et al.[50] In order to create GNPs, an experimental pulse laser beam was focused onto a high-purity gold sheet, which was then placed into deionized water. GNPs were produced in tetrahydrofuran utilizing the pulsed laser ablation approach in another investigation.[51] The average size of produced GNPs was reduced from 11 nm to 6 nm after 30 minutes of ablation. According to the report, these observations were triggered by the quick laser pulse's forced convection flow and shock waves, which fragmented the ablated GNPs even more into tiny sizes.

In recent times, pulsed lasers have been used to treat materials and enhance various chemical reactions. When a target is immersed in a liquid and exposed to pulsed laser energy, the target, and solution form a dispersion due to the formation of cavitation bubbles, shock waves, and secondary photons.[52]

In summary, the use of pulsed lasers in the preparation of GNPs has shown promising results, with researchers achieving high purity and controlled sizes by utilizing the laser ablation approach. The technique offers a reliable and efficient way to synthesize GNPs with potential applications in various fields, including catalysis, biomedicine, and nanotechnology.

2. 8. Biological Method

The biosynthesis of nanoparticles is a straightforward, one-step, green process. The dissolved metal ions are converted into nanometals by biochemical reactions in biological agents. For the production of metal nanoparticles, many biological agents are used, such as plant tissues, fungi, bacteria, etc.[53] To begin the synthesis of GNPs, the biological extract (such as bacterial, fungal, or plant material) is added to the gold (III) chloride ($HAuCI_4$) solution and thoroughly mixed. Gold III (Au^{3+}) is reduced to gold with a neutral charge (Au^0) in the first stage of biosynthesis, and then GNPs are formed as a result of agglomeration of atoms and stabilization in the second step.[53] It's interesting to note that a wide range of bio-compounds, including enzymes, phenols, sugars, and others, can take part in both the stabilization and capping of nanoparticles as well as the reduction of gold.[54]

Eco-friendly extracellular production of metallic GNPs was carried out using leaf extracts from two plants, Magnolia kobus and Diopyros kaki.[55] By employing plant leaf extracts as reducing agents to process an aqueous chloroauric acid ($HAuCl_4$) solution, stable GNPs were created. Scanning electron microscopy SEM and Transmission electron microscopy (TEM) pictures revealed that smaller spherical forms were produced at higher temperatures and leaf broth concentrations, while a mixture of plate (triangles, pentagons, and hexagons) and spherical structures (size, 5–300 nm) were generated at lower temperatures and leaf broth concentrations.[55] In another study, Brazilian Red Propolis extract was used for the biosynthesis of GNPs.[56] The outcomes revealed a potential low-cost green technique to create GNPs with considerable biological characteristics by using Brazilian red propolis. GNPs with spherical shape and an average size of 15 nm were synthesized at 20–50 °C using different volumes of the using Platycodon grandiflorum plant leaf extracts.[57] The diverse phenolic compounds present in the natural extracts has the potential to reduce Au (III).[56,57] Brazilian Red Propolis is a unique type of propolis found in Brazil, specifically in the state of Alagoas, and is known for its distinct red color and potent biological properties.[56,57] Propolis is a resinous substance that bees collect from various plants and trees, which they then modify by mixing it with their enzymes and beeswax. The resulting propolis is used by bees to seal and protect their hives from external threats, such as bacteria, fungi, and other pathogens.

3. Morphology of GNPs

GNPs can be synthesized using various methods, each yielding nanoparticles with different shapes and morphologies. The Brust-Schiffrin method typically results in the formation of spherical GNPs. In this method, gold ions are reduced by sodium borohydride in the presence of a capping agent like alkylthiols, which controls the nanopar-

ticle size and stabilizes the particles in a spherical shape.[22,58] Similarly, the Turkevich method predominantly produces spherical GNPs with sizes ranging from 10 to 100 nanometers.[20,59] In this approach, gold ions are reduced with citrate ions, leading to the formation of well-defined spherical nanoparticles.

Anisotropic GNPs with diverse shapes can be synthesized through the seed-mediated growth method. Depending on the reaction conditions, growth time, and surfactant types, this method can yield gold nanorods, nanostars, nanocubes, and nanospheres. Seed-mediated growth relies on controlling the crystal growth direction and adding seeds with specific crystal facets to induce anisotropic growth and shape control. Electrochemical synthesis of GNPs can also produce various shapes depending on the applied potential and reaction conditions.[27,28] This method can yield gold nanospheres, nanorods, nanowires, and nanoplates. By controlling the potential and electrolytes, researchers can tailor the shape and size of the nanoparticles to suit specific applications.

Template-assisted synthesis involves using templates such as porous materials or dendrimers to guide the formation of unique GNPs shapes. Depending on the structure and dimensions of the templates, this method can produce gold nanotubes, nanocages, or nanowells. Microwave-assisted synthesis is a rapid and controlled method that can produce various shapes of GNPs, including nanospheres, nanorods, and nanoplates. The use of microwave irradiation allows for fast and efficient heating, leading to controlled nanoparticle growth.[60]

To accurately determine the shape of synthesized GNPs, researchers often use advanced characterization techniques such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), or X-ray diffraction (XRD).[2] These techniques allow researchers to visualize and confirm the morphology and size of the nanoparticles, ensuring the desired properties for specific applications. The ability to control the shape of GNPs is crucial as it impacts their physical, chemical, and optical properties, making them suitable for a wide range of applications in catalysis, biomedical imaging, drug delivery, and sensing.

4. Delivery of Therapeutic Agents Using GNPs

Recent years have seen a significant increase in interest in drug delivery techniques for the best and safest delivery of therapeutic agents.[6–71] Nanotechnology-based platforms are among the cutting-edge methods for delivering pharmacologically active compounds that are the subject of extensive research.[5,6,63,64] Diverse categories of nanocarriers have been exploited by researchers to deliver challenging therapeutic molecules. Metal nanoparticles are also in the race and GNPs found many applications in drug delivery apart from other biomedical applications. The following section discusses the recent drug delivery applications of GNPs. However, delivery strategies of protein conjugates and antibodies for the treatment of cancers are not included in this review. A very brief overview of the drug delivery aspects of GNPs is presented in Table 1.

4. 1. Small Molecule Drugs Delivery

GNPs have become increasingly popular for delivering small-molecule drugs during the last few decades. These nanosized carriers provide a suitable method of delivering small compounds as well as biomacromolecules to cells/tissues due to their distinct size-dependent physicochemical properties, flexibility, sub-cellular size, and bio-compatibility.

Table 1. Overview of gold nanoparticles in drug delivery applications.

Therapeutic agent delivered	Objective of delivery	Level of proof	References
5-fluorouracil, and doxorubicin	Targeted delivery	Glioblastoma cell model	[64]
Doxorubicin, and aptamer	Targeted delivery	A549 and 4T1 cells	[65]
Doxorubicin	Extended delivery	MDA-MB-468, βTC-3, and HFb cell lines	[66]
Withaferin A	Targeted delivery	Murine melanoma cells, Chinese hamster ovary, and mouse embryonic fibroblast cells	[67]
Betulinic Acid	Targeted delivery	Human Caco-2, HeLa and MCF-7 cancer cell lines	[68]
Doxorubicin	pH dependent targeted delivery	Human breast, cervical, and hepatocellular carcinoma cell lines	[69]
Linalool	Targeted delivery	breast cancer cell line	[70]
Doxorubicin	Targeted delivery	HeLa cells	[71]
EGFR siRNA	Lung cancer treatment	BEAS-2B, and A549 cells	[72]
Bcl-2 siRNA and doxorubicin	Breast cancer treatment	Triple-negative breast cancer, and MCF7 cell line	[73]
siRNA	Targeted controlled release	Immunodeficient mice bearing A549 tumor xenograft	[74]
siRNA	Laser transfection	Canine pleomorphic adenoma ZMTH3 cells	[75]
siRNA	Topical delivery	Normal human keratinocytes, spontaneously immortalized cells, and HeLa cells	[79]

A pH-responsive drug delivery system composed of GNPs and chitosan with aptamer was reported to deliver anticancer agents (5-fluorouracil and doxorubicin).[65] The drug-loaded GNPs were found monodispersed with a mean size of 196.2 ± 2.89 nm. Cellular internalization of the nanoparticles was also confirmed by transmission electron microscopic investigations.[65] In another intriguing research, GNPs-chitosan conjugates with aptamers were deployed successfully for the targeted delivery of doxorubicin.[66] The tumor specificity of the nano drug delivery system was confirmed in the in vivo studies[66] Surface functionalization of GNPs with chondroitin sulfate and chitosan was successful for extended delivery of doxorubicin.[67] Glucocorticoid receptor-dependent cancer cell-selective cytotoxicity was demonstrated by GNPs conjugated with thiol-modified dexamethasone and withaferin.[68] These compounds also inhibited the growth of an aggressive mouse melanoma tumor, decreased mouse mortality, and prevented tumor cell metastasis. A successful mitochondrial targeting of betulinic acid was reported deploying functionalized GNPs.[69] The effectiveness of mitochondrial targeting was shown by these conjugated GNPs, which significantly inhibited the development of cancer cells. In vitro, the targeted nano complexes recorded IC_{50} values in the range of 3.12–13.2 micro molar (μM) compared to that of the free betulinic acid (BA) (9.74–36.31 μM). High amplitude mitochondrial depolarization, caspase 3/7 activation, and an associated arrest at the G0/G1 phase of the cell cycle were implicated in their modes of action.[69] Spherical-shaped GNPs fabricated with sodium tripolyphosphate as a linking agent and functionalized with chitosan and folate-linked chitosan exhibited a pH-dependent doxorubicin release.[70] The nanoconjugates were found superior to free doxorubicin in terms of chemotherapeutic activities against cancer cell lines. Linalool-loaded GNPs conjugated with a penta peptide Cys-Ala-Leu-Asn-Asn (CALNN) peptide exhibited promising anticancer activities against breast cancer Michigan Cancer Foundation (MCF-7) cell line.[71] Doxorubicin was delivered using GNPs made from Azadirachta indica leaf extract.[72] The GNPs were found to be stable due to the biological capping agents. The resulting complex was found less hazardous to normal cells Madin-Darby canine kidney (MDCK cells) and highly toxic to malignant cells (HeLa cells).[72]

4. 2. Nucleic acids / Small Interfering RNAs Delivery

Small interfering RNAs (siRNAs), among other nucleic acids, are commonly delivered using nanosized carriers in therapeutic settings. Cell membrane interaction is essential for controlling absorption in different delivery modalities. Different portals that enter mammalian cells have different types, sizes, destinations, and cargo fates. A nucleic acid's ability to be released at its site of action and function depends on the mechanism of cellular entry. For delivering siRNA-loaded nanoparticles to specific intracellular locations for a distinct biological impact, small, monodisperse nanoparticles with a defined potential and surface chemistry work best. SiRNA therapies have made great progress, but optimal delivery remains a problem before they can be used clinically.

However, siRNAs are large, negatively charged molecules, which makes it difficult for them to passively diffuse through the cell membrane. They require assistance to enter the target cells. Techniques that focus on changing the size and surface characteristics of nanoparticles make excellent models for understanding drug targeting and cellular absorption. SiRNA and oligonucleotides have been delivered into cells using GNPs.

GNPs were fabricated with biocompatible collagen to improve siRNA loading capacity carrying epidermal growth factor receptor siRNA to treat lung cancer.[73] The conjugated GNPs were biocompatible to normal airway is a well-established and widely used human bronchial epithelial cell line epithelial cells (BEAS-2B) than to cancer cells (A549). The nanocomplexes were comparable or even more efficient, compared with lipofetamine, in carrying siRNA to knock down Epidermal Growth Factor Receptor (EGFR of A549) cells.[73] Tunc et al. (2022) made an intriguing effort by implementing an approach that combined the use of gene therapy and chemotherapy.[74]

For the regulated delivery of siRNAs to the target cells, a nanoconjugate of GNP and oligonucleotides was created.[75] In comparison to the commercial transfection reagent lipofectamine 3000, the core 3D shell nanoconstruct with the outer coating made up of aptamer-incorporated Y-shaped backbone-rigidified triangular DNA bricks was more effective at inducing tumor cell apoptosis. It also effectively reduced the expression of PLK1 mRNA, refers to the messenger RNA (mRNA) molecule that encodes for the PLK1 gene (PLK1 mRNA) and PLK1 protein.[75] In order to successfully bind siRNA at the right weight ratio by electrostatic force and produce well-dispersed nanoparticles, polyethyleneimine-capped GNPs were created.[76] Although confocal laser scanning microscopy observation and fluorescence-activated cell sorting analyses have shown more internalized polyethyleneimine (PEI) and small interfering RNA (siRNA) (PEI/siRNA) complexes in cells, polyethyleneimine-capped GNPs induced more significant and enhanced reduction in targeted green fluorescent protein expression in metastatic ductal adenocarcinoma (MDA-MB-435s) cells with siRNA binding.[76] Topical routes of drug delivery have been greatly exploited for the clinical management of diseases which largely manifest on the skin. However, macromolecules or proteins cannot penetrate through the epidermal barrier when delivered via the transdermal route due to their large size.[77–79] Spherical nucleic acid nanoparticle conjugates were created for simultaneous transfection and gene regulation in another intriguing study.[80] These nanoparticle conjugates didn't

need to be altered or transfected with cationic components to stimulate cellular entrance. Nearly all of the cells in the more than 50 cell lines, primary cells, cultured tissues, and whole organs that these nanostructures entered.[80]

5. Cellular Uptake Mechanism of GNPs

Cellular entry mechanisms, especially related to GNPs, involve various processes by which these nanoparticles are taken up by mammalian cells. GNPs have gained considerable attention in biomedical research due to their unique physicochemical properties and potential applications in drug delivery, imaging, and therapeutics. Understanding the mechanisms of cellular entry is crucial for optimizing GNP-based applications and ensuring their safe and effective use. Endocytosis is a fundamental cellular process through which cells internalize extracellular materials, including nanoparticles, into intracellular vesicles. Several types of endocytosis exist, and the most relevant to GNPs are clathrin-mediated endocytosis, caveolae-mediated endocytosis, and macropinocytosis.[81–83] Clathrin-mediated endocytosis involves the formation of clathrin-coated pits on the cell membrane, which then invaginate and pinch off to form clathrin-coated vesicles containing the GNPs. Caveolae are small invaginations of the cell membrane that play a role in the uptake of certain nanoparticles, including GNPs. In micropinocytosis, the cell engulfs extracellular fluid along with the GNPs into large endocytic vesicles called macropinosomes. For small-sized GNPs (less than 5–6 nm), passive diffusion across the cell membrane can occur. However, this mechanism is not as prevalent for larger-sized GNPs, as their entry is hindered by the cell's lipid bilayer.[84]

Some GNPs can exploit specific cell surface receptors by attaching ligands (e.g., peptides, antibodies) to their surface. This ligand-receptor interaction facilitates receptor-mediated endocytosis, leading to the internalization of the GNP-receptor complex into the cell.[85] Certain types of GNPs, particularly those functionalized with fusogenic peptides or lipids, can undergo direct membrane fusion with the cell membrane. This process allows the GNPs to enter the cell cytoplasm without the need for endocytosis.[86]

It's important to note that the cellular entry mechanisms of GNPs can be influenced by various factors, including their size, shape, surface charge, surface functionalization, and the type of mammalian cell involved.[82,84,85,87] Additionally, the cellular entry pathways may vary depending on the specific GNP formulation and the cellular context.

Researchers continue to investigate these mechanisms to optimize GNP-based applications and improve their targeting, delivery, and safety profiles. Understanding the cellular entry of GNPs is a critical step in harnessing their potential for various biomedical applications.

6. Conclusion

The biocompatibility, variable size, and easy functionalization make GNPs appealing delivery vehicles for nucleic acids. GNP-based covalent and non-covalent nucleic acid carriers alter cellular uptake, endosomal escape, and nucleic acid release. To present, the promise of these systems has primarily been shown in vitro; nonetheless, there remain difficulties to overcome before GNP-nucleic acid conjugates may be used in clinical settings. First, short- and long-term GNP cytotoxicity must be reduced. Numerous studies have shown the biocompatibility of therapeutic NPs using basic cytotoxicity trials.[88–93] However, a full toxicological assessment (cell membrane damage, oxidative stress, genotoxicity, etc.) must be addressed. To reduce negative effects, these vehicles must be targeted to particular organs and tissues. This targeting can be achieved by decorating delivery vehicles with specific antibodies targeting disease cells and (ii) grafting non-interacting functional groups (e.g., polyethylene glycol and zwitter ionic entities) on the surface to avoid plasma protein adsorption, improving pharmacokinetics and evading immune surveillance. Immunological concerns must be investigated before the clinical usage of any novel substance. AuNPs offer a platform with all the features needed to tackle these problems and should continue to provide essential in vitro tools and therapeutically relevant delivery vehicles.

Conflict of Interest

The authors declare no conflict of interest. The authors alone are responsible for the content and writing of the article.

7. References

1. S. Pattnaik, K. Swain, In: Inamuddin, A. M. Asiri, A. Mohammad (Ed.): Applications of Nanocomposite Materials in Drug Delivery, Woodhead Publishing, **2018**, pp. 589–604. **DOI:**10.1016/B978-0-12-813741-3.00025-X
2. K. Pathak, S. Pattnaik, In: S. Bajaj, S. Singh (Ed.): Methods for Stability Testing of Pharmaceuticals. Methods in Pharmacology and Toxicology. Humana Press, New York, **2018**, pp. 293–305. **DOI:**10.1007/978-1-4939-7686-7_13
3. S. Pattnaik, K. Swain, J. V. Rao, T. Varun, K. B. Prusty, S. K. Subudhi, *RSC Adv.* **2015**, *5*, 91960-91965. **DOI:**10.1039/C5RA20411A
4. S. Pattnaik, K. Pathak, *Curr. Pharm. Des.* **2017**, *23*, 467–480. **DOI:**10.2174/1381612822666161026162005
5. S. Pattnaik, K. Swain, P. Manaswini, E. Divyavani, J. V. Rao, V. Talla, S. K. Subudhi, *J. Drug Deliv Sci Technol.* **2015**, *29*, 199–209. **DOI:**10.1016/j.jddst.2015.07.021
6. S. Pattnaik, K. Swain, Z. Lin, *J. Mater. Chem. B.* **2016**, *4*, 7813–7831. **DOI:**10.1039/C6TB02086K

7. Y. C. Yadav, S. Pattnaik, *Drug Dev. Ind. Pharm.* **2023,** *49,* 240–247. **DOI:**10.1080/03639045.2023.2201625
8. S. Chakraborty, M. Dhibar, A. Das, K. Swain, S. Pattnaik, *Recent Adv. Drug Deliv. Formul.* **2023**. **DOI:**10.2174/2667387817666230726140745
9. J. Soutschek, A. Akinc, B. Bramlage, K. Charisse, R. Constien, M. Donoghue, S. Elbashir, A. Gelck, P. Hadwiger, J. Harborth, M. John, V. Kesavan, G. Lavine, R. K. Pandey, T. Racie, K. S. Rajeev, I. Röhl, I. Toudjarska, G. Wang, S. Wuschko, D. Bumcrot, V. Kotellansky, S. Limmer, M. Manoharan, H. P. Vornlocher, *Nature* **2004**, *432*, 173–178. **DOI:**10.1038/nature03121
10. J. C. G. Jeynes, C. Jeynes, M. J. Merchant, K. J. Kirkby, *Analyst* **2013**, *138*, 7070–7074. **DOI:**10.1039/c3an01406a
11. M. Horisberger, J. Rosset, H. Bauer, *Experientia* **1975**, *31*, 1147–1149. **DOI:**10.1007/BF02326761
12. X. Qian, X. H. Peng, D. O. Ansari, Q. Yin-Goen, G. Z. Chen, D. M. Shin, L. Yang, A. N. Young, M. D. Wang, S. Nie, *Nat. Biotechnol.* **2008**, *26*, 83–90. **DOI:**10.1038/nbt1377
13. C. M. Niemeyer, *Nucleic Acids Res.* **2003**, *31*, 1–7. **DOI:**10.1093/nar/gng090
14. D. J. Javier, N. Nitin, M. Levy, A. Ellington, R. Richards-Kortum, *Bioconjug. Chem.* **2008**, *19*, 1309–1312. **DOI:**10.1021/bc8001248
15. S. B. Yaqoob, R. Adnan, R. M. Rameez Khan, M. Rashid, *Front. Chem.* **2020**, 8, 1–15. **DOI:**10.3389/fchem.2020.00376
16. H. Yang, Z. Chen, L. Zhang, W. Y. Yung, K. C. F. Leung, H. Y. E. Chan, C. H. J. Choi, *Small* **2016**, *12*, 5178–5189. **DOI:**10.1002/smll.201601483
17. S. Ramanathan, S. C. B. Gopinath, M. K. M. Arshad, P. Poopalan, V. Perumal, In: S. C. B. Gopinath, F. Gang (Ed.): Nanoparticles in Analytical and Medical Devices, Elsevier, **2021**, pp. 31–43. **DOI:**10.1016/B978-0-12-821163-2.00002-9
18. S. Pattnaik, G. Arun, K. Swain, In: Inamuddin, A. Asiri,(Ed.): Advanced Nanotechnology and Application of Supercritical Fluids. Nanotechnology in the Life Sciences, Springer, **2020**, pp. 1–14. **DOI:** org/10.1007/978-3-030-44984-1_1
19. B. Zheng, L. Qian, H. Yuan, D. Xiao, X. Yang, M. C. Paau, M. M. F. Choi, *Talanta* **2010**, *82*, 177–183. **DOI:**10.1016/j.talanta.2010.04.014
20. J. Dong, P. L. Carpinone, G. Pyrgiotakis, P. Demokritou, B. M. Moudgil, *Kona* **2020**, *37*, 224–232. **DOI:**10.14356/kona.2020011
21. R. Herizchi, E. Abbasi, M. Milani, A. Akbarzadeh, *Artif. Cells Nanomed. Biotechnol.* **2016,** *44,* 596–602. **DOI:**10.3109/21691401.2014.971807
22. P. J. G. Goulet, R. B. Lennox, *J. Am. Chem. Soc.* **2010**, *132*, 9582–9584. **DOI:**10.1021/ja104011b
23. M. T. Reetz, W. Helbig, *J. Am. Chem. Soc.* **1994**, *116*, 7401–7402. **DOI:**10.1021/ja00095a051
24. P. Zhao, N. Li, D. Astruc, *Coord. Chem. Rev.* **2013,** 257*,* 638–665. **DOI:**10.1016/j.ccr.2012.09.002
25. M. T. Reetz, W. Helbig, S. A. Quaiser, U. Stimming, N. Breuer, R. Vogel, *Science* **1995**, *267*, 367–369. **DOI:**10.1126/science.267.5196.367
26. Y. Z. Song, X. Li, Y. Song, Z. P. Cheng, H. Zhong, J. M. Xu, J. S. Lu, C. G. Wei, A. F. Zhu, F. Y. Wu, J. Xu, *Russ. J. Phys. Chem. A* **2013**, *87*, 74–79. **DOI:**10.1134/S0036024413010275
27. C.J. Huang, P .H. Chiu, Y. H. Wang, K. L. Chen, J. J. Linn, C.F. Yang, *J. Electrochem. Soc.* **2006**, *153*, D193. **DOI:**10.1149/1.2358103
28. I. Saldan, O. Dobrovetska, L. Sus, O. Makota, O. Pereviznyk, O. Kuntyi, O. Reshetnyak, *J. Solid State Electrochem.* **2018,** *22,* 637–656. **DOI:**10.1007/s10008-017-3835-5
29. H. Ma, B. Yin, S. Wang, Y. Jiao, W. Pan, S. Huang, S. Chen, F. Meng, *Chem. Phys. Chem.* **2004**, *5,* 68–75. **DOI:**10.1002/cphc.200300900
30. C. Stanglmair, S. P. Scheeler, C. Pacholski, *Eur. J. Inorg. Chem.* ***2014,*** 3633–3637. **DOI:**10.1002/ejic.201402467
31. K. H. Tan, H. A. Tajuddin, M. R. Johan, *J. Nanomater.* **2015**, 537125, 1–8. **DOI:**10.1155/2015/537125
32. C. Ziegler, A. Eychmüller, *J. Phys. Chem C.* **2011**, *115,* 4502–4506. **DOI:**10.1021/jp1106982
33. Q. Yao, X. Yuan, V. Fung, Y. Yu, D. T. Leong, D. E. Jiang, J. Xie, *Nat. Commun.* **2017**, *8,* 927. **DOI:**10.1038/s41467-017-00970-1
34. N. Jara, N. S. Milán, A. Rahman, L. Mouheb, D. C. Boffito, C. Jeffryes, S. A. Dahoumane, *Molecules* **2021**, *26,* 4585. **DOI:**10.3390/molecules26154585
35. J. Castillo, L. Bertel, E. Páez-Mozo, F. Martínez, *Nanomater. Nanotechnol.* **2013**, *3,* 1–6. **DOI:**10.5772/57144
36. G. N. Abdelrasoul, R. Cingolani, A. Diaspro, A. Athanassiou, F. Pignatelli, *J. Photochem. Photobiol. A* **2014**, *275*, 7–11. **DOI:**10.1016/j.jphotochem.2013.10.008
37. K. L. McGilvray, C. Fasciani, C. J. Bueno-Alejo, R. Schwartz-Narbonne, J. C. Scaiano, *Langmuir.* **2012**, *28,* 16148–16155. **DOI:***10.1021/la302814v*
38. V. Mallikarjun, M. Balaji, T. Chandrashekar, A. Shanmugarathinam, G. Bhaskar, H. Roy, *BioNanoSci.* **2023**, *13*. 576–587. **DOI:**10.1007/s12668-023-01102-4
39. M. L. Marin, K. L. McGilvray, J. C. Scaiano, *J. Am. Chem. Soc.* **2008**, *130,* 16572–16584. **DOI:**10.1021/ja803490n
40. P. Kesharwani, R. Ma, L. Sang, M. Fatima, A. Sheikh, M. A. S. Abourehab, N. Gupta, Z.S. Chen, Y. Zhou, *Mol Cancer.* **2023,** *22,* 98. **DOI:**10.1186/s12943-023-01798-8
41. P. T. Huynh, G. D. Nguyen, K. Thi Le Tran, T. Minh Ho, V. Q. Lam, T. V. K. Ngo, *Processes **2021**, 9*, 1–16. **DOI:**10.3390/pr9010112
42. M. A. Bhosale, D. R. Chenna, B. M. Bhanage, *Chemistry Select.* **2017**, *2*, 1225. **DOI:**10.1002/slct.201601851
43. H. J. Chen, D. Wen, *Nanoscale Res. Lett.* **2011**, *6*, 198. **DOI:** org/10.1186/1556-276X-6-198
44. L. Gao, S. Mei, H. Ma, X. Chen, *Ultrason. Sonochem.* **2022**, *83*, 105940. **DOI:**10.1016/j.ultsonch.2022.105940
45. J. A. Fuentes-García, J. Santoyo-Salzar, E. Rangel-Cortes, G. F. Goya, V. Cardozo-Mata, J. A. Pescador-Rojas, *Ultrason. Sonochem.* **2021**, *70,* 105274. **DOI:**10.1016/j.ultsonch.2020.105274
46. A. Shanei, H. Akbari-Zadeh, N. Attaran, M. R. Salamat, M. Baradaran-Ghahfarokhi, *Ultrasonics* **2020**, *102,* 106061. **DOI:**10.1016/j.ultras.2019.106061

47. A. Shanei, M. M. Shanei, *Ultrason. Sonochem.* **2017**, *34,* 45–50. **DOI:**10.1016/j.ultsonch.2016.05.010
48. A. Veeren, M. O. Ogunyankin, J. E. Shin, J. A. Zasadzinski, *Pharmaceutics* **2022,** *14*, 701. **DOI:**10.3390/pharmaceutics14040701
49. F. Sahebi, M. Ranjbar, M. T. Goodarzi, *Appl. Phys. A* **2019**, *125*, 1–8. **DOI:**10.1007/s00339-019-3138-z
50. C. Shalichah, A. Khumaeni, S. Abdulateef, A. Omar, M. Mat Jafri, A. Khumaeni, W. Setia Budi, H. Sutanto, J. Soedharto, *J. Phys. Conf. Ser.* **2017**, *909*, 1–4. **DOI:**10.1088/1742-6596/909/1/012037
51. N. Z. A. Naharuddin, N. Z. A. Naharuddin, A. R. Sadrolhosseini, M. H. A. Bakar, N. Tamchek, M. A. Mahdi, *Opt. Mater. Express* **2020**, *10,* 323–331. **DOI:**10.1364/OME.381427
52. L. Gentile, H. Mateos, A. Mallardi, M. Dell'Aglio, A. De Giacomo, N. Cioffi, G. Palazzo, *J. Nanopart. Res.* **2020**, *23*. 1–12. **DOI:**10.1007/s11051-021-05140-5
53. K. X. Lee, K. Shameli, Y. P. Yew, S. Y. Teow, H. Jahangirian, R. Rafiee-Moghaddam, T. J. Webster, *Int. J. Nanomedicine.* **2020**, *15*, 275–300. **DOI:**10.2147/IJN.S233789
54. E. O. Mikhailova, *J. Funct. Biomater.* **2021**, *12*, 70. **DOI:**10.3390/jfb12040070
55. J. Y. Song, H. K. Jang, B. S. Kim, *Process Biochem.* **2009**, *44*, 1133–1138. **DOI:**10.1016/j.procbio.2009.06.005
56. C. E. A. Botteon, L. B. Silva, G. V. Ccana-Ccapatinta, T. S. Silva, S. R. Ambrosio, R. C. S. Veneziani, J. K. Bastos, P. D. Marcato, *Sci. Rep.***2021**, *11*, 1–16. **DOI:**10.1038/s41598-021-81281-w
57. P. Anbu, S. C. B. Gopinath, S. Jayanthi, *Nanomater. Nanotechnol.* **2020**, *10*. 1–9. **DOI:**10.1177/1847980420961697
58. R. Lévy, N. T. K. Thanh, R. Christopher Doty, I. Hussain, R. J. Nichols, D. J. Schiffrin, M. Brust, D. G. Fernig, *J. Am. Chem. Soc.* **2004**, *126*, 10076–10084. **DOI:**10.1021/ja0487269
59. J. Kimling, M. Maier, B. Okenve, V. Kotaidis, H. Ballot, A. Plech, *J. Phys. Chem. B* **2006**, *110*, 15700–15707. **DOI:**10.1021/jp061667w
60. S. K. Seol, D. Kim, S. Jung, Y. Hwu, *Mater. Chem. Phys.* **2011**, *131*, 331–335. **DOI:**10.1016/j.matchemphys.2011.09.050
61. S. Pattnaik, K. Swain, J. V. Rao, T. Varun, K. B. Prusty, S. K. Subudhi, *RSC Adv.* **2015**, *5*, 91960–91965. **DOI:**10.1039/C5RA20411A
62. S. Pattnaik, K. Pathak, *Curr. Pharm. Des.* **2016**, *23*, 467–480. **DOI:**10.2174/1381612822666161026162005
63. D. S. Panda, N. K. Alruwaili, S. Pattnaik, K. Swain, *Acta Chim. Slov.* **2022**, *69*, 483–488. **DOI:**10.17344/acsi.2022.7370
64. S. Pattnaik, K. Swain, S. Ramakrishna, *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.***2023,** *15*, e1859. **DOI:**10.1002/wnan.1859
65. A. Sathiyaseelan, K. Saravanakumar, A. V. A. Mariadoss, M. H. Wang, *Carbohydr Polym.* **2021**, *262*, 1–14. **DOI:**10.1016/j.carbpol.2021.117907
66. Z. Khademi, P. Lavaee, M. Ramezani, M. Alibolandi, K. Abnous, S. M. Taghdisi, *Carbohydr. Polym.* **2020**, *248*, 1–40. **DOI:**10.1016/j.carbpol.2020.116735
67. T. Chandrashekar, A. Ruhul, M. Jithendar Reddy, G. Amel, E. Talha Bin, B. K. Dey, A. Roy, M. S. Alqahtani, M S. Refat, S.Z. Safi, A.M. Alsuhaibani, M. Asariha, S. H. Kiaie, S. Izadi, F. H. Pirhayati, M. Fouladi, M. Gholamhosseinpour, *BioMed Res. Inter.* **2022**, *2467574*, 1–13. **DOI:** org/10.1155/2022/2467574
68. P. Agarwalla, S. Mukherjee, B. Sreedhar, R. Banerjee, *Nanomed.* **2016**, *11*, 2529–2546. **DOI:**10.2217/nnm-2016-0224
69. O. Oladimeji, J. Akinyelu, A. Daniels, M. Singh, *Int. J. Mol. Sci.* **2021**, *22*, 1–24. **DOI:**10.3390/ijms22105072
70. J. Akinyelu, O. Oladimeji, A. Daniels, M. Singh, *J. Drug. Deliv. Sci. Technol.* **2022**, *67*, 102978. **DOI:**10.1016/j.jddst.2021.102978
71. A. S. S. Majid S. Jabir, Ali A. Taha, Usama I. Sahib, Zainab J. Taqi, Ahmed M. Al-Shammari, *Mater. Sci. Eng. C.* **2019**, *94*, 949–964. **DOI:**10.1016/j.msec.2018.10.014
72. R. Dharmatti, C. Phadke, A. Mewada, M. Thakur, S. Pandey, M. Sharon, *Mater. Sci. Eng. C* **2014**, *44*, 92–98. **DOI:**10.1016/j.msec.2014.08.006
73. A. Y. H. Yu, R. H. Fu, S. hui Hsu, C. F. Chiu, W. H. Fang, C. A. Yeh, C. M. Tang, H. H. Hsieh, H. S. Hung, *Mater. Today Adv.* **2021**, *12*, 100191. **DOI:**10.1016/j.mtadv.2021.100191
74. C. Ü. Tunç, O. Aydin, *J. Drug. Deliv. Sci. Technol.* **2022**, *74*, 103603. **DOI:**10.1016/j.jddst.2022.103603
75. C. Xue, S. Hu, Z. H. Gao, L. Wang, M. X. Luo, X. Yu, B. F. Li, Z. Shen, Z. S. Wu, *Nat. Com.* **2021**, *12*, 1–12. **DOI:**10.1038/s41467-021-23250-5
76. D. Heinemann, M. Schomaker, S. Kalies, M. Schieck, R. Carlson, H. M. Escobar, T. Ripken, H. Meyer, A. Heisterkamp, *PLoS One.* **2013**, *8*, e58604. **DOI:**10.1371/journal.pone.0058604
77. K. Swain, S. Pattnaik, N. Yeasmin, S. Mallick, *Eur. J. Drug Metab. Pharmacokinet.* **2011,** *36,* 237–241. **DOI:**10.1007/s13318-011-0053-x
78. S. Pattnaik, K. Swain, J. V. Rao, T. Varun, S. Mallick, *Medicina* **2015***, 51,* 253–261. **DOI:**10.1016/j.medici.2015.07.002
79. S. Pattnaik, K. Swain, P. Choudhury, P. K. Acharya, S. Mallick, *Int. Braz. J. Urol.* **2009**, *35*, 716–729. **DOI:**10.1590/S1677-55382009000600010
80. D. Zheng, D. A. Giljohann, D. L. Chen, M. D. Massich, X. Q. Wang, H. Iordanov, C. A. Mirkin, A. S. Paller, *Proc. Natl. Acad. Sci. U S A.* **2012**, *109*, 11975–11980. **DOI:**10.1073/pnas.1118425109
81. S. H. Wang, C. W. Lee, A. Chiou, P. K. Wei, *J Nanobiotechnol.* **2010**, *8*, 1–33. **DOI:**10.1186/1477-3155-8-33
82. D. Yılmaz, M. Culha, *Talanta* **2021**, *225*, 122071. **DOI:**10.1016/j.talanta.2020.122071
83. A. M. Alkilany, C. J. Murphy, *J. Nanopart. Res.* **2010**, *12*, 2313–2333. **DOI:**10.1007/s11051-010-9911-8
84. Y. J. Lee, E. Y. Ahn, Y. Park, *Nanoscale Res. Lett.* **2019**, *14*, 2–14. **DOI:** org/10.1186/s11671-019-2967-1
85. A. Kapara, V. Brunton, D. Graham, K. Faulds, *Chem. Sci.* **2020**, *11*. 5819–5829. **DOI:**10.1039/D0SC01255F
86. M. A. Tahir, Z. P. Guven, L. R. Arriaga, B. Tinao, Y. S. S. Yang, A. Bekdemir, J. T. Martin, A. N. Bhanji, D. Irvine, F. Stellacci, A. Alexander-Katz, *Proc. Natl. Acad, Sci. USA.* **2020**, *117*, 18470–18476. **DOI:**10.1073/pnas.1902597117
87. X. Xie, J. Liao, X. Shao, Q. Li, Y. Lin, *Sci. Rep.* **2017**, *7*, 1–9. **DOI:** 1038/s41598-017-04229-z

88. R. Shukla, V. Bansal, M. Chaudhary, A. Basu, R. R. Bhonde, M. Sastry, *Langmuir* **2005**, *21*, 10644–10654. **DOI:**10.1021/la0513712
89. H. R. Ali, M. R. K. Ali, Y. Wu, S. A. Selim, H. F. M. Abdelaal, E. A. Nasr, M. A. El-Sayed, *Bioconjug. Chem.* **2016**, *27*, 2486–2492. **DOI:**10.1021/acs.bioconjchem.6b00430
90. Y. Pan, S. Neuss, A. Leifert, M. Fischler, F. Wen, U. Simon, G. Schmid, W. Brandau, W. Jahnen-Dechent, *Small* **2007**, *3*, 1941–1949. **DOI:**10.1002/smll.200700378
91. A. Chompoosor, K. Saha, P. S. Ghosh, D. J. MacArthy, O. R. Miranda, Z. J. Zhu, K. F. Arcaro, V. M. Rotello, *Small* **2010**, *6*, 2246–2249. **DOI:**10.1002/smll.201000463
92. E. E. Connor, J. Mwamuka, A. Gole, C. J. Murphy, M. D. Wyatt, *Small* **2005**, *1*, 325–327. **DOI:**10.1002/smll.200400093
93. R. Amin, C. Thalluri, A.O. Docea, J. Sharifi-Rad, D. Calina, *eFood* **2022**, *3*, 1–14. **DOI:**10.1002/efd2.33

Povzetek

Nanodelci so običajno nanoskopski materiali z vsaj eno od dimenzij pod 100 nm, ki se uporabljajo v številnih panogah. Najnovejši razvoj na področju nanotehnologije omogoča široko paleto metod za proučevanje in spremljanje različnih medicinskih in bioloških procesov na nanometrski ravni. Nanodelci lahko pomagajo pri diagnosticiranju in zdravljenju bolezni, kot je rak, saj dostavljajo zdravila neposredno do rakavih celic. Uporabljajo se lahko tudi za odkrivanje bioloških označevalcev bolezni v telesu, kar pomaga pri zgodnjem diagnosticiranju. Verjetno je, da bi se nanodelci lahko uporabljali v teranostičnih aplikacijah in pri ciljani dostavi učinkovin. To bi lahko bistveno izboljšalo izide zdravljenja bolnikov ter zmanjšalo količino časa, truda in denarja, potrebnega za diagnosticiranje in zdravljenje bolezni. Prav tako bi lahko zmanjšalo stranske učinke zdravljenja ter zagotovilo natančnejše in učinkovitejše zdravljenje. Nanodelci za uporabo v biomedicini vključujejo polimerne in kovinske nanodelce, liposome in micele, dendrimere, kvantne pike itd. Med nanodelci so se zlati nanodelci (GNP) izkazali kot obetavna platforma za uporabo pri dostavi zdravil. GNP so zaradi svoje odlične biokompatibilnosti, stabilnosti ter nastavljivih fizikalnih in kemijskih lastnosti zelo primerni za dostavo zdravil. Pregledni članek vsebuje poglobljeno razpravo o različnih pristopih k sintezi GNP in aplikacijah za dostavo učinkovin.