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Review Article

Synthesis and application of gold nanoparticles as antioxidants

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Abstract

Non-communicable diseases (NCDs) and premature aging, caused by free radicals, have spurred a demand for extensive research into finding effective antioxidants. Currently, there is an abundance of both natural and synthetic antioxidants, including metal nanoparticles with high antioxidant activity. Among these, gold nanoparticles (AuNPs) stand out as favoured antioxidants because of their minimal toxicity, simple synthesis, and detectability. The antioxidant properties of AuNPs enhance its wide-ranging potential for use in healthcare including applications as anti-aging, anti-inflammatory, and wound healing agents, as well as treatment for various diseases. This review highlights recent progress in the synthesis of AuNPs as antioxidants and method for assessing their antioxidant capacity as well as delves into their mechanism of action and explores their potential health applications. In conclusion, considering the physicochemical and biological properties, along with the benefits and potential challenges for future development, AuNPs are deemed promising and effective antioxidants suitable for clinical applications.

Keywords

Antioxidant, gold nanoparticle, green synthesis, biological methods

Introduction

High pollution, poor dietary habits (including the consumption of junk food and foods high in sugar and fat contents), frequent use of electronic devices and smoking are the identified sources of high exposure of human body to free radicals. These free radicals trigger chain reactions leading to cell destruction due to the oxidative stress. Oxidative stress occurs when the formation of reactive oxygen species (ROS) and the cell's ability to induce effective antioxidant responses are imbalanced, resulting in the accumulation of irreversible damages to lipids, proteins, and deoxyribonucleic acid (DNA). This, in turn, leads to mutations and cell death (Lucia dos Santos Silva et al. 2023). Such conditions may contribute to cardiovascular disease or NCDs including heart disease, diabetes, cancer, and hypertension as well as premature aging (Tuksitha et al. 2018). NCDs are also a leading cause of death worldwide. The World Health Organization (WHO) estimated that approximately 41 million people die each year from conditions such as heart attacks, strokes, cancers, chronic respiratory diseases, diabetes, or mental disorders. These NCDs account for more than 80% of all deaths globally (WHO 2023).

Therefore, the search for substances with the ability to protect the human body from free radical attacks is necessary

to minimize the negative effects resulting from the actions of oxidative stress. Antioxidants are molecules that inhibit the oxidation process of other molecules by donating an electron to the unpaired valence electron within a free radical, thus inhibiting chain reactions of cell destruction (Tuksitha et al. 2018). Moreover, these molecules have the ability to operate through various mechanisms and restore several types of damage at the cellular level (Alaqeel 2023).

The human lifespan is expected to increase by consuming antioxidants as dietary supplements. Moreover, antioxidants play a crucial role in the wound healing process by removing products following inflammatory responses at the wound site (Suntar et al. 2012; Gao et al. 2023). Other applications include preserving foods as well as preventing metal corrosion and rubber vulcanization (Atta et al. 2017; Burenjargal et al. 2023).

In general, antioxidants are categorized into natural and synthetic antioxidants. Natural antioxidants are divided into two major groups, namely enzymatic and non-enzymatic. Most non-enzymatic antioxidants are dietary derived polyphenols carotenoids, ascorbic acid and lipoic acid. Meanwhile, enzymatic antioxidants are those repair enzymes such as SOD (super oxide dismutase), GPx (glutathione peroxidase), GR (glutathione reductase), CAT (catalase) and other metalloenzymes. Moreover, other than these groups, natural antioxidants can also be categorized based on their activity, which are metal chelators, antioxidant regulators, free radical terminators, oxygen scavengers, and singlet oxygen quenchers. On the other hand, synthetic antioxidants are chemically synthesized compounds such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), TBHQ (tert-butylhydroxyquinone), propyl gallate (PG), dodecyl gallate (DG), octylgallate (OG) and ethylene diaminetetraacetic acid (EDTA), that are potentially carcinogenic if consumed at high levels (Atta et al. 2017; Burenjargal et al. 2023).

Recently, nanomaterials have been discovered as a promising antioxidant material with higher effectiveness and efficiency. Several types of nanomaterials, including organic materials (i.e., melanin, lignin), metal oxides (i.e. cerium oxide) or metal-based nanoparticles (i.e. gold, platinum, silver) exhibit intrinsic redox activity associated with radical trapping, superoxide dismutase-like, and catalase-like activities. Among these nanoparticles, gold is of particular interest due to its unique electronic and optical properties, high physical and chemical stability, and high surface energy (Alex and Tiwari 2015; Chen et al. 2022; Aili et al. 2023; Sharifi-Rad et al. 2023). Apart from being relatively non-toxic and inert, AuNPs could be easily synthesized as demonstrated in many studies (Hammami et al. 2021; Li et al. 2023b).

Different methods have been explored in synthesizing AuNPs and assessing their antioxidant property. Each method yields distinct structures and morphologies of nanoparticles, potentially influencing the strength of antioxidant activity. Fig. 1 displays various shapes of AuNPs including hexagonal, pentagonal, and triangular forms, as well as spherical which is the predominant form.

AuNPs exhibit high catalytic activity in some oxidation reactions, forming strong complexes with biomolecules, and possessing unique electrical and optical properties, making them applicable in diverse fields (Yakimovich et al. 2008; Mikhailova 2021). These nano-based antioxidants offer many advantages owing to their higher stability compared to small molecules, and the ability to avoid rapid decomposition of metabolism and reach specific target cells (Valgimigli et al. 2018; Hammami et al. 2021). Furthermore, AuNPs can scavenge free radical species directly through catalytic reaction on their surface, inducing an interaction between the unpaired electron from the free radical and the conduction band electron of AuNPs, resulting in enhancement of antioxidant property (Beurton et al. 2019; Aili et al. 2023). Therefore, AuNPs are widely used in various applications such as biosensors, drug delivery systems, cell-based cancer therapies, antibacterial and antioxidant agents. Therefore, this review summarizes recent advancements in the synthesis of AuNPs, methods for assessing their antioxidant capacity as well as mechanisms of action and potential applications in human health.

Synthesis

Nanoparticles can be synthesized using physical, chemical, biological or hybrid methods (Kulkarni 2014; Abdullaeva 2017; Rajagopal and Parvathi 2017; Roy et al. 2018). Nevertheless, classification into "top down" and "bottom up" approach is commonly used to classify nanoparticle synthesis methods (Binns 2010; Murty et al. 2013; Alex and Tiwari 2015; Abdullaeva 2017; Kanchi and Ahmed 2018; Jamkhande et al. 2019; Ramalingam 2019). Fig. 2 elaborates on the synthesis method of AuNPs limited to the production of AuNPs that could exhibit antioxidant activity.

The top-down approach is a subtractive method that aims to reduce the particle size of bulk materials into nanoparticles using nanofabrication equipment. External experimental parameters are adjusted and controlled to obtain AuNPs with the desired particle shapes and physical characteristics (Biswas et al. 2012b; Ramalingam 2019). On the other hand, the "bottom up" approach is a method that assembles nanoparticles from atoms, molecules or smaller particles to produce more complex nanoscale assemblies or directed assemblies through covalent or supramolecular interactions (Biswas et al. 2012a; Iqbal et al. 2012; Thota and Crans 2018; Jamkhande et al. 2019).

In the last decade, the synthesis of AuNPs developed for antioxidant agents has predominantly followed the 'bottom-up' approach, largely due to the drawbacks associated with the 'top-down' approach. The identified drawbacks encompass increased costs, heightened susceptibility to imperfections in smaller features and surface structures, decreased conductivity, undesired catalytic activities, crystallographic damages, and impurity contamination. (Iqbal et al. 2012; Roy et al. 2018).

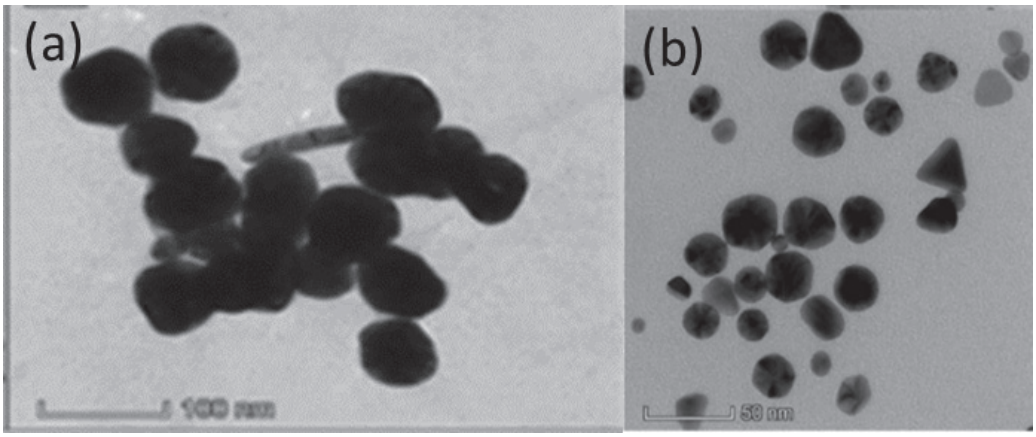

Figure 1. TEM images of **a**. Spherical and pentagonal shapes; **b**. Triangular, hexagonal and spherical shapes of AuNPs. Reproduced by permission from the references (Nor Azlan et al. 2020b; Mohammad et al. 2022).

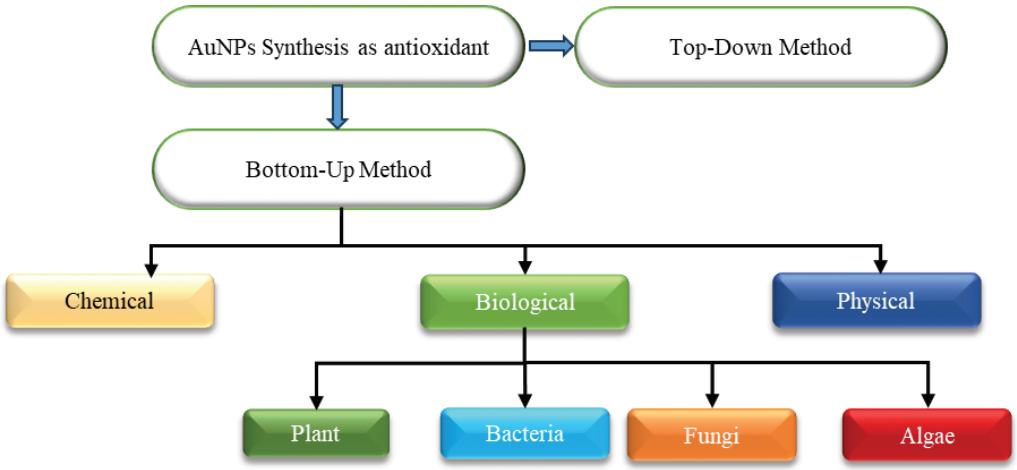

Figure 2. Synthesis methods of AuNPs for the potential use as antioxidants.

Furthermore, the "bottom up" approach is preferred due to its advantages, including zero waste or the absence of unused materials, the production of very fine individual nanostructures with narrow size distributions, homogeneous chemical compositions, and minimal defects. The method is simple, fast, and cost-effective, offering the ultimate limits of miniaturization and enabling the production of a broader range of functional nanostructured materials through chemical synthesis (Biswas et al. 2012a, Iqbal et al. 2012; Murty et al. 2013; Goyal 2017). The common 'bottom-up' approach used to synthesize AuNPs for antioxidant activity includes chemical and biological methods.

Top-down method

Electrical explosion wire

This method is a top-down technique to produce nanoparticles by exposing metallic wire to a high density current pulse in a liquid, air or gaseous media (Kotov 2003; Cho et al. 2007; Lázár et al. 2018). In this method, AuNPs are formed by exposing 0.1 mm of gold wire to 3 kV voltage in distilled water (Sul et al. 2010). In the initial phase, the wire is melted and disintegrated into either small droplets or even evaporated atoms within a few microseconds (Lázár et al. 2018). Subsequently, a highly dispersed suspension of AuNPs is formed. Several advantages have been noted for electrical explosion wire in a liquid media as compared to the air or gas media: (1) a non-oxide metal powder can be generated without resorting to the vacuum process, (2) it is feasible to retain the non-oxide phase in the concluding stages of applications, and (3) high dispersibility of the nanopowder in dispersive liquids (Cho et al. 2007). The AuNPs obtained from this method were reported to exhibit a remarkable antioxidant activity by reducing the generation of ROS in response to Receptor Activator of Nuclear Factor-B Ligand (RANKL) and upregulated RANKL-induced glutathione peroxidase-1 (Gpx-1) in the bone marrow-derived macrophages (BMM) of mice (Sul et al. 2010).

Combination of electrochemical and chemical method

The antioxidant AuNPs can be synthesized through a combination of electrochemical and chemical techniques. In the first phase, electrochemical process is conducted in a three-compartment cell at room temperature and the

process is controlled by a potentiostat. The cell is consisted of a bulk of Au substrates as the working electrode, a platinum sheet as the counter electrode and a KCL-saturated silver-silver chloride (Ag/AgCl) rod as the reference electrode. The electrolyte solution used is a deoxygenated aqueous solution containing salt and natural chitosan (Yu et al. 2011).

Following the initial phase, the cyclic voltammetry method is applied to the electrochemical cell with a specific voltage and deposition cycle. After this electrochemical process, complexes of $AuCl_4^-$ are present in the electrolyte solution. The subsequent phase involves a chemical technique to obtain pure AuNPs by boiling the solution. During this stage, the AuNPs are formed. After cooling, the solution containing these AuNPs is purified by placing it in an ultrasonic bath and then centrifuging it for a certain period of time. In this method, chitosan plays a crucial role in obtaining zerovalent AuNPs. In a study that employed this method, the resulting AuNPs with a size of 10 nm was found to exhibit a comparable antioxidant activity to vitamin C (Yu et al. 2011).

Bottom-up method

Chemical method

The chemical method consists of reduction process and stabilization (Herizchi et al. 2016). Examples of reducing agents are citric and oxalic acid, borohydrides, polyols, sulfites, and hydrogen peroxide. Reducing agents provide electrons to reduce gold ions (Au^{3+} and Au^{+}) to the electric state of nanoparticles (Au^0). Meanwhile, stabilizing agents work by introducing a repulsive force to control the rate, final size or geometric shape of nanoparticles, thereby preventing their aggregation. Several chemical substances, including sulfur ligands (especially thiolates), phosphorus ligands, trisodium citrate dihydrate, polymers, surfactants, and other agents, are employed as stabilizing agents. Moreover, the stabilizing agents can be the same substance as the reducing agents (Daruich De Souza et al. 2019; Jamkhande et al. 2019).

Limited studies evaluated antioxidant activity of chemically synthesized AuNPs using both electrochemically reduction and chemical reduction methods. In the electrochemical reduction method, AuNPs as antioxidant agent were successfully synthesized by varying the deposition potential (Suliasih et al. 2024) and scan rate (Suliasih et al. 2023). This technique is recognized for its facile and cost-effective nature in metallic nanoparticles preparation (Budi et al. 2010, 2016, 2020), making it a promising approach for future fabrication of AuNPs. Regarding the chemical reduction method, to our best knowledge, only Turkevich method has been used in synthesizing AuNPs for the purpose of obtaining antioxidant activity. This method was first developed by Turkevich in 1951 and since then, it has been modified by several other researchers (Kimling et al. 2006; Pong et al. 2007; Ojea-Jiménez et al. 2011; Herizchi et al. 2016). The method involves the reaction between hydrogen tetrachloroaurate ($HAuCl_4$) and citrate in boiling water. Citrate acts as an agent for reducing gold ions into AuNPs and stabilizing the resultant nanoparticles from further particle growth, preventing the formation of large particle aggregates (Yeh et al. 2012). This agent can also be replaced with ascorbic acid and tannic acid (Hussain et al. 2020). Strictly controllable process parameters such as concentration, pH and temperature have been noted as one of its drawbacks (Hussain et al. 2020). Recently, this method has been demonstrated to successfully produce AuNPs with the particle size of 2.7 nm and exhibited a high antioxidant activity of approximately 73% inhibition as determined by the DPPH method (Beurton et al. 2019). In a different study, the production of AuNPs with the size of 10.3 nm and 31.3 nm AuNPs exhibited notable antioxidant properties as evaluated by the DPPH method. The IC_{50} values for these nanoparticles were found to be 6.201×10^{-9} and 2.217×10^{-10} mol/L, respectively (Li et al. 2023b).

Biological method

Biological methods have been widely applied for synthesizing AuNPs for their antioxidant activity. This method, also known as biosynthetic or green synthesis method, involves the use of biological agents, ranging from plant extracts, bacteria, fungi, and algae. This approach has gained significant attention due to its benefits, including high biocompatibility for medical purposes, environmentally friendly characteristics, use of non-toxic solvents, pollution-free operation, and absence of toxic and hazardous substances (Nasrollahzadeh et al. 2015; Katas et al. 2018; Kalimuthu et al. 2020; Ying et al. 2022). However, the biological method faces limitations related to the availability of biological materials, lengthy synthesis time, challenges in controlling the growth of living organisms, and high variability in particle size. These factors collectively pose obstacles for large-scale production (Jamkhande et al. 2019; Ying et al. 2022). In general, this method involves two key techniques (Fig. 3):

Bioreduction: This process aims to reduce metal ions into a biologically stable form using reducing agents found in microorganisms or plant extracts such as amino acids, flavonoids, aldehydes, sugars, amines, ketones, phenols, carboxylic acids, proteins, pigments, alkaloids, terpenoids and other reducing agents (Kanchi and Ahmed 2018). The obtained nanoparticles can be harvested from the contaminated sample to produce stable and inert nanoparticles.

Biosorption: This technique involves the binding of metal cations to the cell wall of certain bacteria, fungi and plants in aqueous media prior to the reduction of metal ion in the presence of enzymes (Kanchi and Ahmed 2018). However, several pieces of evidence have shown that this biosorption technique is mainly applied for biological synthesis using bacteria and fungi (Pantidos 2014; Jamkhande et al. 2019; Qamar and Ahmad 2021).

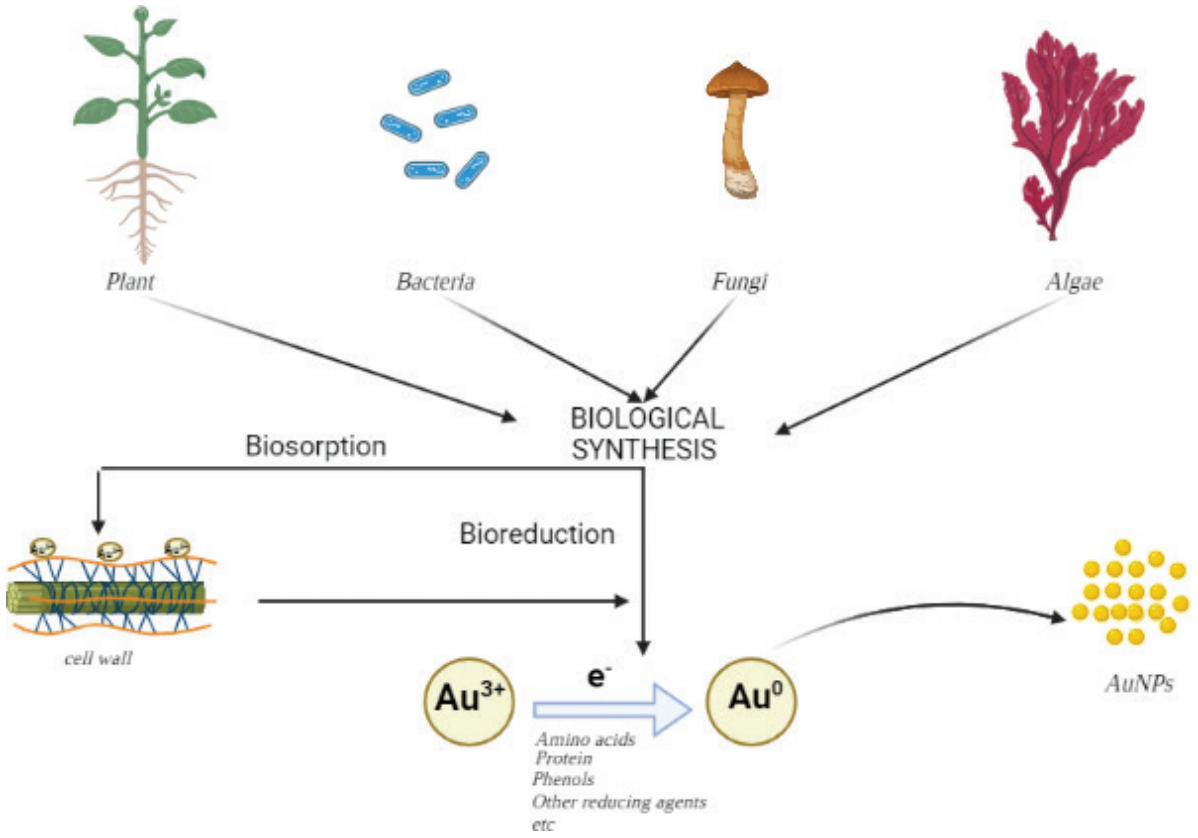

Figure 3. Biological technique to produce AuNPs.

Plant extracts

Generally, several processes are involved in preparing plants prior to AuNPs synthesis. These include the procurement of various parts of plants, cleaning to remove contaminants, drying, pulverizing to acquire fine powder, aqueous extraction, filtering to remove large particles and obtain fine grained particles and synthesis (Fig. 4). One of the protocols that is commonly used is one-pot hydrothermal chemical reduction method. This method is commonly applied in preparing plant-AuNPs as antioxidants. This involves mixing a plant extract and metal salt ($HAuCl_4$) to form plant-AuNPs with different morphologies. This process typically takes from a few minutes to several hours. Variation in certain reaction conditions can be applied, including changes in pH and temperature, as well as adjustments to the amount of $HAuCl_4$ and plant extracts (Chen et al. 2019; Qiao and Qi 2021).

Plant extracts serve as both reducing and stabilizing agents in the fabrication of metal nanoparticles. Common phytochemicals in the plant extracts with these roles include polysaccharides, polyphenols, alkaloids, flavonoids, reducing sugars, phenols, amino acids, vitamins, ketones, and proteins. In this reaction, the phytochemicals in the plant extracts will reduce Au^{3+} to Au^0 and then mediate and stabilize the resulting AuNPs by covering the outer surface of the AuNPs to prevent agglomeration (Qiao and Qi 2021).

Moreover, pH of the plant extract solution significantly influences the yield of AuNPs synthesis. Evidence has shown that a higher pH induces easier reduction of Au^{3+}, resulting in a higher yield of AuNPs (Oueslati et al. 2020). The nature and ratio of the phytochemical fractions play an important role for the formation of nanoparticles, in addition to the pH of reaction medium. Furthermore, the type of plant extract may influence the shape of the obtained AuNPs. For example, the use of hydrosoluble crude extracts produced nanoflower shaped particles, whereas the concentrate of flavonoid produced smaller monodispersed spherical nanoparticles (Ben Haddada et al. 2020; Kalimuthu et al. 2020).

The reduction of gold ions requires high temperatures. Previous studies have indicated that the optimal reduction of gold ions occurs at the temperature range of 80–90 °C. Higher temperatures have been shown to significantly decrease nanoparticle size, whereas lower temperatures result in larger particles (Mohammed Fayaz et al. 2009; Wang et al. 2016). The concentration of gold ions may also influence the characteristics of AuNPs, with a higher concentration of gold ions capable of increasing both particle size and distribution (Wu and Chen 2010).

Table 1 presents a list of antioxidant activity of AuNPs synthesized using plant extracts as the reducing and stabilizing agents, employing one-pot hydrothermal chemical reduction method. The majority of AuNPs were spherical in shape, with particle sizes ranging from 2 to 64 nm. The antioxidant activities are commonly expressed as IC_{50}, a value indicating the concentration of antioxidant required to effectively scavenge 50% of the initial DPPH radicals (Olugbami et al. 2014; Francis et al. 2018).

Table 1. List of AuNPs with antioxidant activity synthesized using plant extracts.

No	Name of the plant species	Part of the plant	Shape	Average size (nm)	IC_{50} value (µg/mL)	Reference
1.	*Hubertia ambavilla*	Leaf and flower	flower	50	16.5	(Ben Haddada et al. 2020)
2.	*Acalypha indica*	leaf	spherical	20	16.25	(Boomi et al. 2020)
3.	*Albizia amara*	leaf	nearly triangle, with a few having hexagonal	34–64	25.25 ± 0.43	(Balasubramani et al. 2017)
4.	*Alpinia nigra*	leaf	spherical	21.52	52.16	(Baruah et al. 2018)
5.	*Allium sativum L.*	leaf	spherical	19	231	(Liu et al. 2021b)
6.	*Jatopra curcas. L*	Leaf	irregular	17.12	16.59	(Francis et al. 2018)
7.	*Terminalia arjuna*	Bark	spherical and triangular	less than 50	10	(Suganthy et al. 2018)
8.	*Coleus forskohlii*	root	spherical	10–30	60	(Dhayalan et al. 2018)
9.	*Achillea biebersteinii*	flower	spherical	8	261.84	(Mobaraki et al. 2021)
10	*Panax ginseng*	Whole plant	spherical	5–10	1.96	(Jiménez Pérez et al. 2017)
11	*Chaenomeles sinensis*	fruit	spherical icosahedral with core	smaller than 40	725.93	(Oh et al. 2018)
12	*Thymbra*	Leaf	Irregular	about ~ 20	125	(Liu et al. 2021a)
13	*Sambucus wightiana*	Whole plant	trigonal, cubic, hexagonal, and polygonal	15.96	37.23	(Khuda et al. 2021)
14	*Centaurea behen*	leaf	spherical	below 50	25	(Abdoli et al. 2021)
15	*Kaempferia parviflora*	rhizome	well dispersed and smooth surfaced spherical	44 ± 3	94.5 ± 2.49	(Varghese et al. 2021)
16	*Garcinia kola*	seed	spherical	2 - 17	520	(Anadozie et al. 2023)
17	*Ocimum basilicum*	flower	spherical	19–44	228	(Jiang et al. 2023)

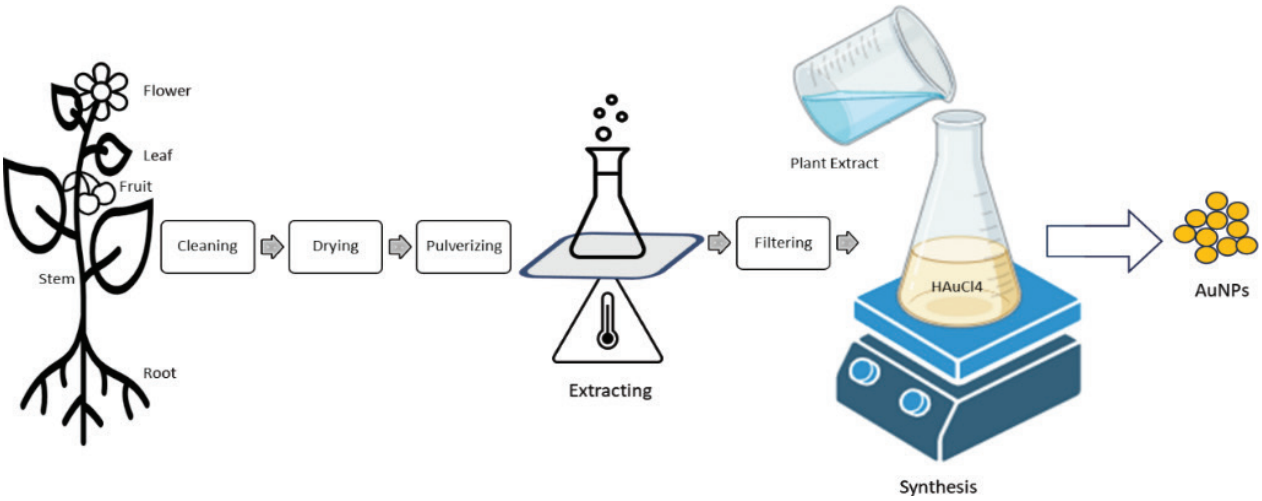

Figure 4. One-pot hydrothermal chemical reduction synthesis to produce AuNPs.

The obtained IC_{50} values for antioxidant activity ranged from 1,96 – 725,93 µg/mL. The antioxidant activity of AuNPs is reported to be higher than that of the plant extract alone because the antioxidant compounds from plant extracts are adsorbed onto the active surface of nanoparticles (Reddy et al. 2015; Godipurge et al. 2016; Vinosha et al. 2019; Sunayana et al. 2020; Liu et al. 2021b; Mobaraki et al. 2021; Muniyappan et al. 2021). The surface reaction and the high surface area-to-volume ratio of a nanoparticle may also influence the interaction and scavenging activity of free radicals, resulting in a higher antioxidant activity (Kumar et al. 2021). Contrarily, some studies showed the opposite effect, as the antioxidant activity of the plant extract alone was higher than that of AuNPs. This phenomenon was expected to be due to the reduction of bioactive phytochemical concentration, such as alkaloids, flavonoids and phenolic compounds present in the extract during nanoparticle formation, thus decreasing the free radical scavenging activity of the nanoparticles (Kuppusamy et al. 2015; Nakkala et al. 2016; Chahardoli et al. 2018; Abdoli et al. 2021).

Bacteria

In this method, the synthesis of nanoparticles involves extracellular biologically active substances of bacteria (Manivasagan et al. 2015). The excellent properties of bacteria, such as being easy to cultivate, manipulate and facilitate rapid multiplication, are also useful for the synthesis of AuNPs (Jamkhande et al. 2019). However, only a small number of bacteria can be used for selectively reducing metal ions (Kalimuthu et al. 2020). Enterococcus species have been demonstrated to produce AuNPs with spherical-shaped particles with the particle size range of 8–50 nm. The AuNPs also exhibited a significant antioxidant activity (33.24–51.47% inhibition at concentration of 1–40 µg/ml) (Oladipo et al. 2017). A similar result was reported by Markus et.al., who synthesized AuNPs with Lactobacillus kimchicus (Markus et al. 2016).

Furthermore, AuNPs demonstrated greater antioxidant activity when compared to ascorbic acid, particularly the highest level of activity was observed in AuNPs characterized by spherical particles with an average size of 11.57 ± 124 nm, which were synthesized using Nocardia sp. (Manivasagan et al. 2015). Nocardia sp. GTS18 has also been used to synthesize AuNPs with a particle size of 40–45 nm and DPPH radical scavenging activity ranging from 26.81 ± 6.3% to 60.90 ± 2.9% at the concentration ranging from 100 to 2000 µg/mL (Könen-Adigüzel et al. 2018). Similar to plant extracts, the antioxidant activity of AuNPs is expected to be enhanced with the increasing particle surface area that facilitates the catalytic reaction involving protein molecules from bacteria (Oladipo et al. 2017).

Fungi

Fungi have been used for AuNPs synthesis, as the fungal mycelial mesh can withstand higher flow pressure and agitation in bioreactors or other chambers compared to other microbial systems (Kalimuthu et al. 2020). Due to their extensive secretory components, fungi can produce nanoparticles extracellularly and support the reduction and capping of nanoparticles (Gericke and Pinches 2006). Moreover, biosynthesis with fungi is more effective than the one with bacteria due to the advantages, including the presence of mycelia, which provides an increased surface area. Furthermore, the fact is that fungi secrete significantly higher amounts of proteins compared to bacteria, thereby it enhances the synthesis productivity (Pantidos 2014).

AuNPs produced from this method exhibited a comparable antioxidant activity to the strong antioxidant, ascorbic acid. Elegbede et al. reported that the antioxidant activity of AuNPs, fabricated using Aspergillus niger and Trichoderma longibrachiatum, displayed the inhibition rates ranging from 42.91% to 53.79% at concentrations of 10–100 µg/ml. This result was compared to the antioxidant activity of ascorbic acid, which ranged from 39.03% to 64.42% at concentrations of 2–10 µg/ml. The observed antioxidant activity of AuNPs could be attributed to the functional groups of bioreductant molecules attached to the nanoparticle surfaces (Elegbede et al. 2020). In a different study, the antioxidant activity of AuNPs synthesized by the marine endophytic fungus (Penicillium citrinum) was also found to be comparable to that of the standard ascorbic acid (Manjunath et al. 2017).

Algae

AuNPs can be also synthesized using algae. Marine algae could produce highly stable AuNPs extracellularly in a relatively shorter time compared to other biological methods (Kalimuthu et al. 2020). This method has successfully produced AuNPs with considerably higher antioxidant activity than the algae extract alone. The AuNPs were mostly in triangular and spherical nanostructures, with an average particle size of 16 nm, and they were well dispersed without any presence of agglomeration (Vinosha et al. 2019). In a different study, biosynthesized AuNPs were produced using an edible freshwater epilithic red algae, Lemanea fluviatilis (L.). The AuNPs exhibited polydispersity, with nearly spherical particles ranging in size from 5 to 15 nm. Nevertheless, these AuNPs remarkably demonstrated strong antioxidant activity, with an SC50 (the sample weight required to scavenge 50% of DPPH) measured at 18.10 mg (Sharma et al. 2014). In summary, algae and its compounds exhibit robust antioxidant properties. When combined with AuNPs and other antioxidants from diverse sources, such as plant extracts, a potent synergistic antioxidant effect is anticipated.

Physical method

The physical approach has also been documented as a means for the synthesis of AuNPs via the molecular beam epitaxy process (Leu et al. 2012). Molecular beam epitaxy is a physical process to produce nanoparticles on a substrate by using a molecular beam under ultra-high vacuum conditions (Fig. 5). The nanoparticles growth takes place through the interaction of molecular beam sources at the substrate which is maintained at a high temperature and pressures of residual gases lower than 10^{-7} Pa (Herman and Sitter 1996; Martín-Palma and Lakhtakia 2013; Goyal 2017; Asahi and Horikoshi 2019).

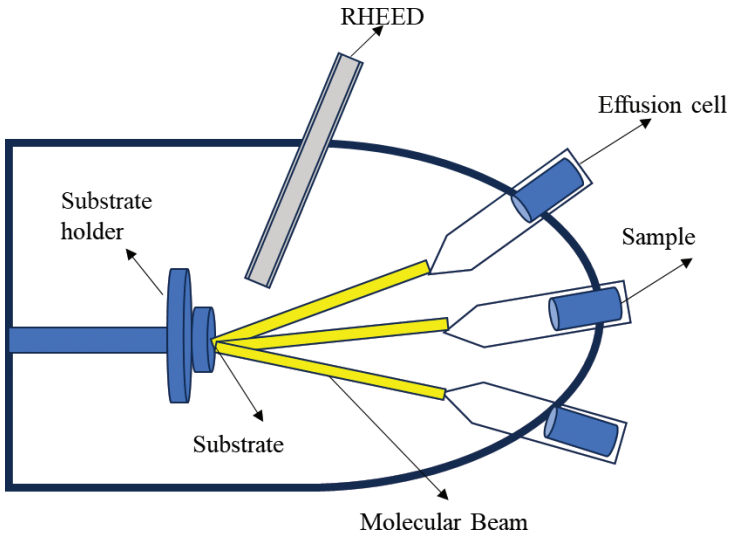

Figure 5. Illustration of Molecular Beam Epitaxy Ultra High Vacuum Chamber.

In this method, the material of gold bulk is placed into the effusion cell and heated to their sublimation points. Then, the Au target is vaporized to the atomic level by an electrically gasified method under a vacuum. Molecular beams are then generated in this process thereby directed toward the substrate. In close proximity to the substrate, these beams can undergo chemical reactions with each other or with other introduced gaseous species within the vacuum chamber. Subsequently, the resulting reaction products condense to form a layer of AuNPs on the substrate. Reflection high-energy-electron diffraction (RHEED) is used for in situ monitoring of the growing nanoparticles (Leu et al. 2012; Martín-Palma and Lakhtakia 2013; Asahi and Horikoshi 2019). The combination of these AuNPs with epigallocatechin gallate (EGCG) and α-lipoic acid (ALA) was shown to markedly enhance the healing of cutaneous wounds in mice by virtue of their anti-inflammatory and antioxidative properties (Leu et al. 2012).

Method for evaluating antioxidant capacity of AuNPs

In vitro studies

DPPH ([2,2-di(4-tert-octylphenyl)-1-picrylhydrazyl) method

The antioxidant activity of AuNPs is commonly measured by the DPPH method, a simple technique that requires spectrophotometric measurement of sample absorbance. The measurement is based on the ability of antioxidants to donate electrons that neutralize DPPH radicals (Munteanu and Apetrei 2021). DPPH is a stable free radical and available commercially. The assessment of antioxidant activity is determined by measuring the decrease in absorbance at a wavelength of 515 nm. The result is often described as $IC_{50,}$ the required concentration to decrease 50% of initial DPPH concentration effectively (Shahidi and Zhong 2015; Li et al. 2023b). Furthermore, this approach has garnered considerable interest owing to its efficacy in demonstrating the scavenging activity of AuNPs. DPPH molecules readily adsorbed to the AuNPs' surface via an electron transfer mechanism, resulting in the formation of a complex known as AuNPs-DPPH. This phenomenon arises from the robust affinity properties of AuNPs for the unpaired electron on the nitrogen atom of the DPPH molecule (Razzaq et al. 2016).

Li et al. conducted a study to investigate the antioxidant activity of flavonols, AuNPs, and flavonol-AuNPs using the DPPH method. Their findings revealed that flavonol-AuNPs exhibited a significantly higher antioxidant activity compared to both flavonol and AuNPs when tested individually. The highest IC_{50} was 4.383 × 10–11 mol/L for myricetin-AuNPs, a member of flavonoids (Li et al. 2023b). Another study investigated the antioxidant activity of AuNPs synthesized using brown seaweed (Spatoglossum asperum). These 20 nm-sized AuNPs significantly scavenged free radical of the DPPH molecules, exhibiting 73.21% inhibition at a concentration of 50 μg/ml (Govindaraj et al. 2023).

ABTS (2,2-azinobis (3-ethylbenzothiazoline-6-sulphonic acid) method

This method applies the same underlying principle as the DPPH assay, but it focuses on distinct radical species and is commonly referred to as the Trolox Equivalent Antioxidant Capacity (TEAC) assay. In this assay, the effectiveness of antioxidants in neutralizing the stable radical cation ABTS is assessed. The ABTS radical is subsequently transformed into a colorless product. The extent of this transformation is quantified by measuring the discoloration of a blue-green chromophore at a wavelength of 734 nm (Shahidi and Zhong 2015). The TEAC value is determined by comparing the degree of discoloration caused by a compound to that induced by Trolox (Arts et al. 2004). When employing the ABTS assay for gold nanoparticles (AuNPs), the measurement relies on the AuNPs' capacity to donate electrons, thereby neutralizing the ABTS radical species. The green-synthesized AuNPs with a peel extract of sweet lime fruit (Citrus limetta Risso) showed a remarkable antioxidant activity, as evaluated by the ABTS method, revealing an IC_{50} of 54.39 μg/ml (Sivakavinesan et al. 2022). Moreover, an IC_{50} of 44.81 μg/ml was obtained from mycosynthesized AuNPs produced using Aspergillus terreus (BalaKumaran et al. 2022).

Hydroxyl radical (H_2O_2) scavenging method

This method belongs to the same group of radical scavenging assays as the two previously mentioned. The antioxidant's scavenging activity is assessed by measuring the reduction in absorption of H_2O_2 molecules at a wavelength of 230 nm (Gulcin 2020). This method is effective for measuring the antioxidant capacity of AuNPs, owing to their intrinsic catalase-like activity, which involves donating electrons to H_2O_2 molecules, leading to the decomposition of H_2O_2 and the production of oxygen (He et al. 2013; Sivakavinesan et al. 2022). AuNPs fabricated through the green synthesis of fungal xylanases from Aspergillus niger and Trichoderma longibrachiatum exhibited inhibition percentages ranging from 74% to 96% at concentrations of 1–40 μg/ml. Furthermore, other biosynthesized AuNPs by the peel extract of sweet lime (Citrus limetta Risso) also demonstrated an excellent antioxidant activity, with a 50% H_2O_2 scavenging activity observed at a concentration of 56.58 μg/ml (Elegbede et al. 2020; Sivakavinesan et al. 2022).

Nitric oxide radical (NO·) scavenging method

In this method, the antioxidant activity was assessed by measuring the antioxidant ability to prevent the production of NO· through the nitration of 4,5-diaminofluorescein. The scavenging values are calculated as the percentage inhibition of the oxidation of 4,5-diaminofluorescein, which is directly proportional to the concentration of the NO· scavenging compound (Gulcin 2020). Biosynthesized AuNPs using Vitex negundo leaf extract have been

discovered as potent scavengers of nitric oxide, exhibiting an inhibition value of 83% at a concentration of 100 µg/ml. This phenomenon demonstrates the ability of AuNPs to donate electrons to NO·, supported by a dehydrated environment (Sunayana et al. 2020). Meanwhile, another researcher emphasized the influence of phenolic groups, such as flavonoids and flavanols, present in the Vitex negundo leaf extract used to synthesize the AuNPs. This study revealed an IC_{50} value of 70.45 µg/ml for the AuNPs (Veena et al. 2019).

In vivo studies

This method usually involves testing animals, such as rats, mice, rabbits, etc., to evaluate the antioxidant action of AuNPs within living cells. Several studies have demonstrated the remarkable antioxidant effect of AuNPs. Toxicological evaluation is also conducted in these animal models due to the understanding that the effects may depend on the particle size and shape as well as the surface charge and modification (Jia et al. 2017). Safety information of AuNPs obtained from studies on animal models is hence important to allow further development and its application in humans.

Rats model

The antioxidant effect of AuNPs on the early stage of collagen-induced arthritis has been studied in rats. In this study, the antioxidant action of intraarticularly injected 13 nm or 50 nm AuNPs significantly increased the cellular catalase activity without causing negative effects on hematological indices. These AuNPs reduced the production of malondialdehyde (MDA). This MDA is the end product of polyunsaturated fatty acid peroxidation in cells, and its level serves as a standard indicator of oxidative stress (Mehanna et al. 2022). In addition, these AuNPs also significantly up-regulated the activity of CAT, the primary antioxidant responsible for the direct elimination of ROS (Kirdaite et al. 2019). The antioxidant effects of AuNPs have also shown great impact on diabetes and wound healing on male albino rats that were induced with a single intraperitoneal injection of streptozotocin (Ponnanikajamideen et al. 2019).

Toxicological evaluation was also carried out for different sizes of AuNPs (10 and 50 nm) for the exposure duration of 3 days (Abdelhalim and Moussa 2013). AuNPs were intraperitoneally administered in rats for evaluating their effects on the liver and kidneys by monitoring several biochemical parameters including aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alanine transaminase (ALT), alkaline phosphatase (ALP), urea (UREA) and creatinine (CREA). Based on the results obtained, AuNPs altered the liver enzymes to a certain extent, suggesting the need for liver protection during the treatment with AuNPs. In contrast, UREA and CREA showed no significant alterations, indicating no toxicity effects were detected for the kidneys. In a more recent study, biodistribution of different sizes AuNPs (10, 30 and 60 nm) were investigated in Wistar rats and the organ distribution (liver, spleen, kidneys and intestine) was dependent on the particle size (Lopez-Chaves et al. 2018). Higher toxicity effects were observed for the smallest particles due to the high accumulation that led to the overproduction of free radicals and ROS from protein carbonylation, lipid peroxidation and DNA damages.

Mice model

The antioxidant effect of AuNPs in restraining hyperglycemic conditions has been explored in diabetic mice models. This finding showed the significant inhibitory effect of AuNPs against ROS generation during hyperglycemia induced oxidative stress. In addition, the diabetic mice treated with AuNPs showed a significant decrease in lipid peroxidation compared with diabetic control group mice, indicating an additional benefit of using AuNPs in treating hyperglycemia (BarathManiKanth et al. 2010). Studies have shown that lipid peroxidation can lead to the production of reactive lipid species, which in turn may cause damage to cellular structures. (Zamboni 2008). Another study reported a significant anti-inflammatory and antioxidative effects of AuNPs in mice suffering from asthma. In the study, researchers found evidence that AuNPs could reduce catalase activity and malondialdehyde (MDA) levels in the lung tissues. This reduction in catalase activity and MDA levels is associated with the occurrence of oxidative tissue injury in mice. The study highlights the potential impact of AuNPs on lung health and oxidative stress. (Serra et al. 2022). Moreover, Ok Joo-Sul, et.al found that AuNPs could inhibit Receptor Activator of Nuclear Factor-κB Ligand (RANKL) induced osteoclast (OC) formation in vitro by decreasing ROS production and upregulating the antioxidant enzyme Gpx-1 in mice. RANKL is a key differentiation factor for OC, and has been reported to induce the production of ROS via the RANK-TRAF6 signal pathway (Sul et al. 2010).

For toxicological evaluation in mice, AuNPs (12.5 nm) were considered as a non-toxic agent after repeated administration intraperitoneally for 8 days at 40, 200, and 400 µg/kg/day (Lasagna-Reeves et al. 2010). Despite AuNPs were accumulated the most in the liver followed by kidneys and spleen, no significant organ abnormalities were detected. More recently, the subchronic toxicity study revealed the non-toxicity of AuNPs (53 nm) at 0.2, 2, and 20 mg/kg after repeated dose of oral administration to mice for 90 days. Other than minor infiltration in the kidneys and altered platelet indices at the highest dose in the male and female mice respectively, no obvious abnormalities, mortality and adverse effects were seen (Sun et al. 2021). When coating with other polymers such as polyethyleneimine (PEI) and polyethylene glycol (PEG), the level of distribution was significantly enhanced, with the highest accumulation observed in the liver and spleen after a single dose was administered to the mice (5 mg/kg) (Ozcicek et al. 2021). Middle levels of accumulation of these nanoparticles (50 nm) were seen in the blood tissues, kidneys and heart while the least were seen in the brain.

Rabbits model

Gold nanorods (AuNRs), sized at 50 nm, exhibited remarkable antioxidant activity in male rabbits after intravenous repeated-dose treatment over a 15-day period. This was evidenced by the elevated levels of SOD, GPx and CAT, coupled with a reduction in MDA levels. Therefore, it is concluded that these AuNRs could effectively inhibit the elevated ROS generation and lipid peroxidation (Mehanna et al. 2022). The remarkable antioxidant effect of AuNPs on dry eye disease in a rabbit model has been also reported (Li et al. 2019). In a different study involving New Zealand White rabbits, the acute toxicity and biodistribution of AuNPs were investigated. These rabbits, with implanted liver Vx2 tumours, received intravenous injections of 5 nm and 25 nm AuNPs. The results showed no evidence of renal, hepatic, pulmonary, or other organ dysfunction. On the other hand, after administration of 25 nm AuNP, white blood cell concentration was observed to be increased, while most other blood parameters remained unchanged. AuNPs also accumulated in the spleen, liver, and Vx2 tumours, but not in other tissues. In summary, smaller AuNPs were more evenly distributed throughout tissues, suggesting their potential as effective tools for medical therapy (Glazer et al. 2011).

Mechanism of action of AuNPs as antioxidants

The antioxidant capacity of AuNPs was reported to derive from the interaction between antioxidant compounds from the biological agents and surface area of AuNPs that works synergistically. However, it has been noted that metal nanoparticles may possess an inherent antioxidant effect owing to their unique surface properties. The inherent antioxidant property of AuNPs manifests through two distinct techniques: the preventive mechanism and the chain-breaking mechanism as depicted in Fig. 6. Within the preventive action, two specific mechanisms emerge: catalase-mimic behavior and superoxide (SOD)-mimic behaviors (He et al. 2013; Li et al. 2015; Valgimigli et al. 2018; Jo et al. 2020). Catalase-mimic behavior occurs only at neutral or basic pH values. This behavior acts by reducing H_2O_2 to H_2O and O_2. Meanwhile, SOD-mimic behavior traps superoxide radical and releases H_2O_2 and O_2. In a recent study, AuNPs had been shown to display catalase and peroxidase-like activity when their core was decorated with a loose and branched platinum shell. These particles hold the potential to mitigate ischemia-reperfusion injury in the kidney by reducing cellular apoptosis, modulating cytokine release, and inhibiting inflammasome production and signalling (Feng et al. 2022). These findings support the antioxidant properties of AuNPs, which enable them to scavenge ROS and exhibit characteristics akin to multiple enzymes.

Furthermore, the chain-breaking mechanism demonstrates the ability of AuNPs to simultaneously transfer

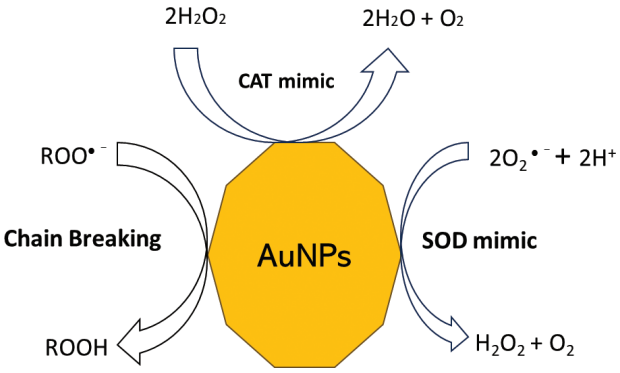

Figure 6. Mechanism of action of AuNPs as antioxidants.

electrons and protons to alkylperoxyl radicals (ROO·), resulting in the formation of ROOH from cleavable O-H groups (Valgimigli et al. 2018; Shah et al. 2022). To scavenge alkylperoxyl radicals effectively, a supply of both an electron and a proton is necessary. This can be achieved either simultaneously by an H-atom donating antioxidant, or separately by an electron-donating antioxidant in the presence of a protic solvent (Valgimigli et al. 2018). It has been also reported that AuNPs could enhance the antioxidant capacity of other antioxidants. The AuNPs can be grafted with well-known potent antioxidants to create antioxidant-functionalized AuNPs, which exhibit a higher antioxidant capacity. This process involves the absorption of the antioxidant onto the surface of AuNPs, leading to an increase in their chemical reactivity (Nie et al. 2007; Valgimigli et al. 2018).

Correlation between physicochemical properties of AuNPs and antioxidant activity

The antioxidant activity is the catalytic activity of AuNPs that emerges from the surface of these nanoparticles. Therefore, the physicochemical properties of AuNPs should contribute significantly to their antioxidant activity (Bano et al. 2023). Another researcher has also stated that the remarkable physical properties, particularly the optoelectronic properties, as well as chemical and biological properties of AuNPs, can be finely tuned by changing the size, shape, surface chemistry, and aggregation state (Oueslati et al. 2020).

The physiochemical characteristics of AuNPs are very diverse, particularly the particle shape and size. The shapes include triangle, hexagon, octahedron, cells, nanospheres, wells, stars, and nanorods that are produced from various methods of synthesis. Mehanna et.al investigated the effect of AuNPs shape on the antioxidant activity in male rabbits. This study showed that gold nanorods (AuNRs) significantly exhibited higher antioxidant activity than gold nanosphere (AuNSs) (Mehanna et al. 2022). Nevertheless, studies investigating the influence of the shape of AuNPs on their antioxidant activity are still limited. Moreover, Table 1 shows that the spherical shape is the

dominant variant especially those reported in antioxidant research. However, these data are not comparable to each other, so it cannot be conclusively determined whether the shape of AuNPs has an effect on their antioxidant activity.

Commonly, particle size has a significant impact on the catalytic activity of AuNPs. Smaller particles can induce more catalytic activity because they create a larger surface area, which may allow more active sites to interact with free radicals (Bano et al. 2023). Several studies have demonstrated that larger AuNPs exhibit reduced antioxidant potency when compared to their smaller counterparts (Kumar et al. 2018; Akintelu et al. 2021). This evidence showed that the performance of AuNPs is affected mostly by the particle size.

Potential uses of AuNPs in terms of its antioxidant activity

Skin aging

AuNPs possess the capability to scavenge ROS, making them suitable for managing pathological conditions associated with the presence of ROS. Abundance of ROS present in the body may harm cellular functions especially skin tissues (Kammeyer and Luiten 2015). Moreover, AuNPs are known to prevent formation of skin wrinkles by competing with carbohydrates for binding to amino acids like lysine and arginine, resulting in the inhibition of advanced glycosylation end products (AGEs) formation that causes loss of skin elasticity and subsequently, formation of wrinkles (Pageon 2010). Recent research has also demonstrated the potential antioxidant capacity of AuNPs in protecting human skin cells (dermoprotection) from UV-A irradiation. UV-A radiation, characterized by longer wavelengths, is known to contribute to skin aging (Ben Haddada et al. 2020).

Wound healing

AuNPs hold promise as wound healing agents. When a wound disrupts the protective skin epithelial layer, whether with or without damage to underlying connective tissues (such as muscle, bone, or nerves), the antioxidative abilities of AuNPs come into play. These abilities are crucial for promoting fibroblast growth and minimizing cell death, both essential processes in wound healing (Ovais et al. 2018). Additionally, AuNPs exhibit the capability to modulate the secretion of various proteins, including IL-8, IL-12, VEGF, and TNF-α, all of which play pivotal roles in wound healing. Leveraging this capacity, combining gold with antibacterial peptides and polylactic-co-glycolic acid (PLGA) materials has been found to enhance wound healing in rat models (Dong et al. 2024). Numerous studies have also demonstrated successful outcomes for AuNPs in accelerating wound healing in animal models (Akturk et al. 2016; Lau et al. 2016; Ovais et al. 2018; Ponnanikajamideen et al. 2019; Boomi et al. 2020; Hu et al. 2020; Cherng et al. 2022).

Other pathological conditions

AuNPs are associated with antioxidant activity, which can address various pathological conditions linked to oxidative stress caused by RO including atherosclerosis, inflammatory and neurodegenerative diseases (Mikhailova 2021).

Atherosclerosis

AuNPs have been proposed as regulators of lipoprotein levels. They can facilitate the replication of high-density lipoprotein (HDL) and synthesize HDL-like molecules. These applications hold potential for both diagnosis and treatment of atherosclerosis (Younis et al. 2021). AuNPs also demonstrated a remarkable ability to restore the levels of superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) in RAW264.7 cells treated with high glucose. Furthermore, they effectively inhibited radical production in macrophage cells exposed to high glucose. This capacity holds significant promise in minimizing atherosclerosis and managing diabetic disease (Rizwan et al. 2017).

Inflammatory conditions

Immune cells become activated during inflammation, leading to continuous production and release of free radicals, resulting in oxidative stress. AuNPs, acting as enzymatic antioxidants, effectively inhibit the generation of free radicals in phagocytes (Agarwal et al. 2019; Li et al. 2023a). Research has shown that AuNPs-embedded ceria nanoparticles (Au/CeO2) successfully treat inflammatory bowel disease in mice due to their enzymatic catalytic antioxidant properties (Li et al. 2023a). Additionally, AuNPs synthesized from Suaeda japonica leaf extract exhibit excellent effectiveness in reducing proinflammatory cytokines and inflammatory mediator production (Kwak et al. 2022). Moreover, the antioxidant effect of AuNPs makes them valuable for diseases related to inflammation, such as rheumatoid arthritis (Hornos Carneiro and Barbosa 2016; Jaaffer and Al-Ogaidi 2022). In animal and human models, AuNPs also significantly suppress inflammation in the early stages of erosive immune-mediated polyarthritis (Kirdaite et al. 2019).

Neurodegenerative diseases

In neurodegenerative diseases, it has been observed that AuNPs have the capacity to inhibit the pro-inflammatory reactions in a cell line of microglia. This property of AuNPs is advantageous in promoting the repair and regeneration of the central nervous system (Mikhailova 2021). Another study observed the advantageous effects of AuNPs in the treatment of Alzheimer's disease (AD), one of the neurodegenerative diseases. In this case, AuNPs have the ability to regulate antioxidant levels in the brain, facilitate mitochondrial repair, and enhance the removal of ROS within the mitochondria. This mechanism ultimately leads to a reduction in oxidative stress in the brains of patients with Alzheimer's disease (Aili et al. 2023).

Bone loss

AuNPs have been found to play a role in reducing bone loss by inhibiting osteoclast formation. Osteoclasts are specialized cells responsible for breaking down bone tissue, which is crucial for normal bone remodelling. However, in pathological conditions, these cells can contribute to bone loss due to their heightened resorptive activity (Boyce et al. 2009). Recent evidence suggests that AuNPs achieve this effect by interfering with the production of RANKL (Receptor Activator of Nuclear Factor Kappa-B Ligand). RANKL is a key player in osteoclast differentiation and has been linked to increased production of ROS. By reducing ROS production and enhancing the expression of the antioxidant enzyme Gpx-1, AuNPs may offer protection against bone loss associated with post-menopause (Sul et al. 2010).

Hyperglycaemia

The potential application of AuNPs (Fig. 7) in preventing oxidative stress and their adverse effects, induced at hyperglycemic conditions has opened up ways for a new resource of cost economic alternative in the treatment of diabetic progression (BarathManiKanth et al. 2010). Diabetes mellitus disease is characterized by inadequate insulin secretion and variable levels of insulin resistance, leading to elevated blood glucose concentrations. This high glucose levels have been observed to induce the production of ROS, which are implicated in the development of metabolic dysregulation and chronic complications. AuNPs as antioxidant agent has been proven to have capability to scavenge ROS and inhibit ROS production by increasing antioxidant defence enzyme in streptozotocin induced diabetic mice (BarathManiKanth et al. 2010). Evidence of the ability of AuNPs bioconjugated with aminoguanidine to inhibit glycation reactions in diabetic rats has also been reported (Ahmad et al. 2021). Several studies have also reported the remarkable activity of AuNPs in diabetic animal models, particularly in relation to their antioxidant activity (Ponnanikajamideen et al. 2019; Nor Azlan et al. 2020a; Sekar et al. 2022). Moreover, AuNPs possess significant anti-oxidative properties on several chronic pathological conditions, including cancers (Mobaraki et al. 2021; Jiang et al. 2023), sepsis (Di Bella et al. 2021), heart disease (Chouke et al. 2022) and asthma (Al-Radadi 2023).

Figure 7. Potential clinical applications of AuNPs as antioxidants.

Constraints of AuNPs applications as antioxidants

Scaling up and stability

Scaling-up of AuNPs from laboratory approach to meet the commercial demand provides a great challenge. This is primarily due to the difficulty in controlling and modifying particle size at larger or industrial scale (Akintelu et al. 2021). Another challenge is the AuNPs stability in biological medium since their properties may change due to the influence of biological media environment and their biotransformation. Previous evidence showed that when AuNPs are administered into the body, the particles will be internalized by cells and accumulated into the lysosomes (Balfourier et al. 2020a, 2020b). The plasmonic property of AuNPs was strongly affected by the surface surroundings and the conditions pertaining to their aggregation which are highly influenced by the acidic condition in the lysosome. Moreover, the optical properties of AuNPs may also be altered as they tend to aggregate within the lysosome (Balfourier et al. 2020a). Capping agents have been demonstrated to enhance the stability of AuNPs. Hydrophobic drugs such as dexamethasone and thiol-terminated polyethylene glycol are reported capping agents with a proven capability to enhance AuNPs in biological medium (Manson et al. 2011; Rossi et al. 2016).

Relative toxicity

Moreover, the toxicity is still a matter of concern even though AuNPs are claimed to be relatively less toxic than other metals such as silver (Khan et al. 2019; Ali et al. 2021; Hammami et al. 2021; Sani et al. 2021). The toxicity of AuNPs in animal models has been extensively studied, yet conflicting reports persist. Several factors contribute to this discrepancy, including variations in study protocols, experimental methods, and the physicochemical properties of AuNPs. The physicochemical characteristics of AuNPs such as size, shape, targeting ligand, surface chemistry, elasticity and chemical composition have been reported to influence their toxicity (Khan et al. 2019; Pinho et al. 2022). In addition, toxicity of AuNPs is related to the cell or tissue type, concentration used, and administration route (Pinho et al. 2022). To ensure the safe utilization of AuNPs, it is imperative to address these conflicting findings.

Physicochemical characteristics

Smaller particles may induce higher toxicity than larger ones. Furthermore, it has been reported that positively charged particles demonstrate a higher level of toxicity compared to their negatively and neutrally charged particles (Khan et al. 2019). A study investigated the impact of particle shape on cellular uptake in human hepatoma cells. The results indicated that star-shaped particles demonstrated lower uptake, while spherical particles exhibited higher uptake (Xia et al. 2019). This information sheds light on the significance of particle shape in influencing cellular interactions and drug delivery processes.

Time of exposure and organ accumulation

The toxicity of AuNPs is also related to the time of exposure and retained in organs. Prolonged exposure may lead AuNPs to interfere with the metabolism and disrupt energy homeostasis, resulting in cytotoxicity. Moreover, systemic AuNPs may accumulate in the liver and causes hepatotoxicity if retained for a long time (Sahoo and Hormozi-Nezhad 2023). Numerous in vivo and in vitro studies have been conducted to investigate the toxicity of AuNPs (Sani et al. 2021). A study on Wistar rats showed that AuNPs of 20 nm altered gene expression after two months when administered via intravenous injection (Balasubramanian et al. 2010). In a different study, AuNPs with the size of 13 nm, coated with PEG (MW 5000), were injected intravenously into BALB/c mice. After 7 days, these particles caused acute inflammation and apoptosis in the liver (Cho et al. 2009). Toxicity effects on BALB/c 3T3 fibroblast cells have been reported, which exhibited DNA damage. Another study on MG63 cells also showed low long-term toxicity effects (Sani et al. 2021). Intravenous administration of AuNPs with diameters ranging from 15 to 200 nm in mice resulted in negatively metal oxidative accumulation of particles in various organs, predominantly in the liver, spleen, lung, heart, brain, and pancreas. This research demonstrated that smaller particles exhibited a greater propensity for accumulation in organs, with the potential to breach the blood-brain barrier and concentrate within the brain tissues.

Future prospects of AuNPs as antioxidants

AuNPs have indeed exhibited sophisticated antioxidant properties, offering a wide range of healthcare applications. These include anti-aging, anti-inflammatory, and wound healing effects. Additionally, AuNPs have shown promise in treating various diseases, such as atherosclerosis, cancers, neurodegenerative conditions, diabetes, rheumatoid arthritis, and asthma. It is expected that as more and more AuNP systems show promising results at the research level, these materials will be in the interest of industry players to invest in R&D for industrial scale and commercial production. It can also be used as an alternative agent, replacing antioxidant agents that have been obsolete. It has been predicted that the market for metal nanoparticles will grow to $40.6 billion By 2027 (Nadaf et al. 2022). Therefore, more in-depth mechanistic studies of oxidative stress in vivo and clinical evaluation in humans are needed to develop AuNPs as antioxidant agents for therapeutic applications.

AuNPs have been shown to possess advanced antioxidant properties. These properties present a broad spectrum of healthcare applications, including but not limited to anti-aging, anti-inflammatory, and wound healing capabilities. Moreover, they hold promise in the treatment of various conditions such as atherosclerosis, cancer, neurodegenerative diseases, diabetes, rheumatoid arthritis, and asthma.

Conclusion

AuNPs are shown to be a promising antioxidant for various applications. AuNPs synthesized via biological methods are shown to exhibit a good antioxidant property which is comparable to other common antioxidants such as ascorbic acid. Synthesized AuNPs also showed a stronger antioxidant capacity than their counterparts, the plant extracts alone. Phytochemicals or proteins that are embedded to AuNPs surfaces are reported to contribute to the enhanced antioxidant capacity. However, the antioxidant capacity of nanoparticles may also come from the inherent property of the nanoparticle surface. More research is needed to explore this inherent property in AuNPs.

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