



Review Article

Plant based Gold Nanoparticles and Penetration through Blood Brain Barrier

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ABSTRACT

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The blood brain barrier (BBB) is designated as one of the most vital shielding mechanism placed in central nervous system (CNS) regulating brain microenvironment. Selectively allowing only essential molecules like micro soluble lipids through capillary membrane while obstructing the passage to toxins and pathogens. This mechanism is termed as essential for normal well being of brain health; however, it also poses extreme challenges during disease state hindering the adequate drug delivery to effected region. In recent years there have been number of researches specifically exploring efficient drug delivery methods via penetration through BBB such as structural modifications in prodrugs via using liposome, micelles, dendrimers, carbon nanotubes, niosomes, beta cyclodextrin carriers etc or inducing osmotic disruption in BBB etc. However, most of such strategies failed to provide substantial proof to desired site specific activity across BBB. The current review here discusses plant mediated Gold nanoparticles (AuNP's) drug delivery system as a future transpiring non-invasive system for brain related diseases and disorders as neuroprotective agents. The scope of plants based AuNPs will be elaborated considering their recent advancement to research activity and propensity to devise into therapeutics with ability to act across BBB as targeted drug therapy. This could be a remarkable progress exploring green synthesis protocols towards gold nanoparticles, reformulating equivalent novel strategies to in place conventional methods for cerebral diseases.

1. Introduction

Despite of recent advancement to understanding of complex pathophysiological pathways associated to multiple neurological disorders, there have been exponential rise in its cases in recent years. This might be largely due to inefficient drug delivery system i.e. inadequate action of therapeutics to the specific disease site across the blood brain barrier (BBB). BBB is considered as the major obstacle to cerebral drug transport, acting as a natural barrier to most molecules entering to the brain. This mechanism is essential for neuro protection, however pours immense challenge to device and develops compatible treatment strategies that could deliver desired response across BBB[1,2]. Hence, unique drug delivery approaches are needed with the idea of utilizing macro molecules with the ability to deliver high drug concentration locally and nominal systemic adverse effects. Plant based gold nanoparticles (AuNP's) could be an ideal choice for brain targeting[3].

Nanotechnology in recent years has been immensely popular amongst researchers, for more efficient, alternative and

targeted drug delivery system. Nanoparticles derived through this technique; mostly bear controlled structure, unique features and potency to act as desired. However, the chemical & physical methods involved for their production are quite costly and unsafe for the environment. Considering to the fact, utilization of greener means for producing nanomolecules would add credit to much more environmentally friendly, on hazardous and biologically safe substances for treating human diseases[4-6]. Plant derived gold nanoparticles could be a potential method to physically and chemically produce desired greener bionanoparticles with the capacity to penetrate across BBB and therefore, they might lay the steadfast foundation to treatment of multiple neurological disorders. Moreover, plants and their extracts give large window to scale up the synthesis of nanoparticles.

At present, evidences suggest that multiple numbers of plants and their extracts have been used for synthesis of gold nanoparticles in order to meticulously target neurological disorders, especially with gruelling etiology and low therapeutics access. Plant such as *Medicago sativa*[7,8], *Hypericum perforatum*[9-11], *Ocimum gratissimum*[12],

Punica granatum[13-16], *Salix alba*[17-19], *Vitis vinifera*[20,21], *Stevia rebaudiana*[22,23], *Sesbania grandiflora*[24], *Allium noeanum*[25], *Hibiscus sabdariffa*[26,27] etc (Table 1) offer magnificent prospects to well organized AuNPs synthesis. However, for brain targeting due to high selectivity and complexity of BBB, our focus would be specific on those plant based AuNPs which bears regulated sizes up to macro level and therefore could act across BBB.

2. Plant Based Gold Nanoparticles

Plant based gold nanoparticles are not only the greener way to device neuroprotective therapeutics but are also cost

effective and relatively reproducible. Plant extracts play dual role as both stabilizing and reducing agents during the synthesis of nanoparticles thus are facilitating the drafting of AuNP's in variable shapes & sizes (Figure-1). The variability in shape & sizes of AuNPs firmly impacts their chemical and physical properties and their ability across BBB. Plant based AuNP's Shapes such as nanospheres; nanocages, nanoprism etc are most commonly synthesized on larger scale however the AuNPs with triangular shapes shows remarkable optical properties in comparison to others. Considering, the fact to extensive ability of AuNPs in site specific drug delivery, therapeutics, extremely fine size with larger surface area, stability, zero cytotoxicity and exceptional optical, chemical properties could lead to an revolution to treatment strategies for brain related disorders like Alzheimer, Tumours, Parkinson's etc[28-30].

Table No. 1: Multiple plant based AuNPs and their reported neuroprotective activities (*in-vivo/vitro*)

Plant for AuNPs	Extract Part	Shape & Size of AuNPs	Techniques to Characterization	Neuroprotective Effects (<i>in vitro/vivo</i>)	References
<i>Cudrania tricuspidata</i>	Roots	Spherical & 23.3 nm	DLS, ZP, HR-TEM, EDR, FT-IR, XRD, UV-VIS	Brain Tumour/Glioblastoma	[31]
<i>Vitex negundo</i>	Leafs	Spherical rod shaped & 20-80 nm	UV-VIS, SEM, DLS, FTIR	Antiinflammatory/Antioxidative brain activity	[32]
<i>Saudi origanum</i>	Leafs	Spherical & 5-61 nm	SEM, DLS, XRD, FTIR, TEM	Self regenerative antioxidant activity, anti-inflammatory effects	[33]
<i>Tussilago farfara</i>	Flower Buds	Spherical & 18 nm	SPR, UV-VIS, XRD, FTIR	Anti-inflammatory, Anti-tumour/Cancer, Alzheimer disease.	[34]
<i>Vaccinium shrubs/Vitis labrusca</i>	Most part of the Plant	Spherical & 18-94 nm	FTIR, UV-VIS, TEM, XRD, DLS	Anti-inflammatory, Anti tumour, Alzheimer's disease, Parkinson's disease, Schizophrenia	[35]
<i>Ephedra sinica</i>	Whole Plant	Spherical & 24-58 nm	DLS, FTIR, XRD, UV-VIS, ZP	Antineuroinflammatory effects mediated neurodegenerative disorders like front temporal dementia, amyotrophic lateral sclerosis, Alzheimer, Huntington & Parkinson disease.	[36]
<i>Paeonia moutan</i>	Root	Spherical & 100 nm	UV-VIS, FTIR, HR-TEM, EDAX and XRD analysis	Neurodegenerative disorders: Parkinson Disease	[37]
<i>Terminalia arjuna</i>	Leaf	Spherical & 15-30 nm	UV-VIS, TEM, EDX	Antioxidant, anticholinesterase, and antiamyloidogenic effects	[38]
<i>Panax ginseng</i>	Root	Spherical & 5-70 nm	DLS, ZP, HR-TEM, EDR, FT-IR, XRD	Anti-Acetylcholinesterase/ butyrylcholinesterase activity in neurodegenerative disorders	[39]
<i>Mucuna pruriens</i>	Seeds	-	FT-IR, TEM, XRD, UV-VIS	Parkinson's Diseases, Improving behavioural & motors coordination,	[40]
<i>Hypericum perforatum</i>	Leaves	Spherical	DLS, ZP, HR-TEM, EDR, FT-IR, XRD	Behavioural impact/reduction in stress induce anxiety and oxidative damage to the brain	[41]
<i>Kalopanax cortex</i>	Stem/bark	Spherical & 41-54nm	UV-VIS, XRD, SPR, ZP, HTEM, FTIR	Protects human neuronal cells from oxygen glucose deprivation and reoxygenation induced neuronal cell injury via NRF2 signalling pathways and heme oxygenase-1 gene knockdowns.	[42]

Abbreviations: DLS (Dynamic light scattering), HR-TEM (High Resolution Transmission Electron microscopy), SAED (Selected area electron diffraction), FFT (Fast Fourier transform), EDR (Energy dispersive spectroscopy), XRD (X-ray diffraction), and FT-IR (Fourier-transform infrared spectroscopy), SPR (Surface Plasmon resonance), EDX (Energy-dispersive X-ray spectroscopy).

3. Biosynthesis of Plant Based Gold Nanoparticles

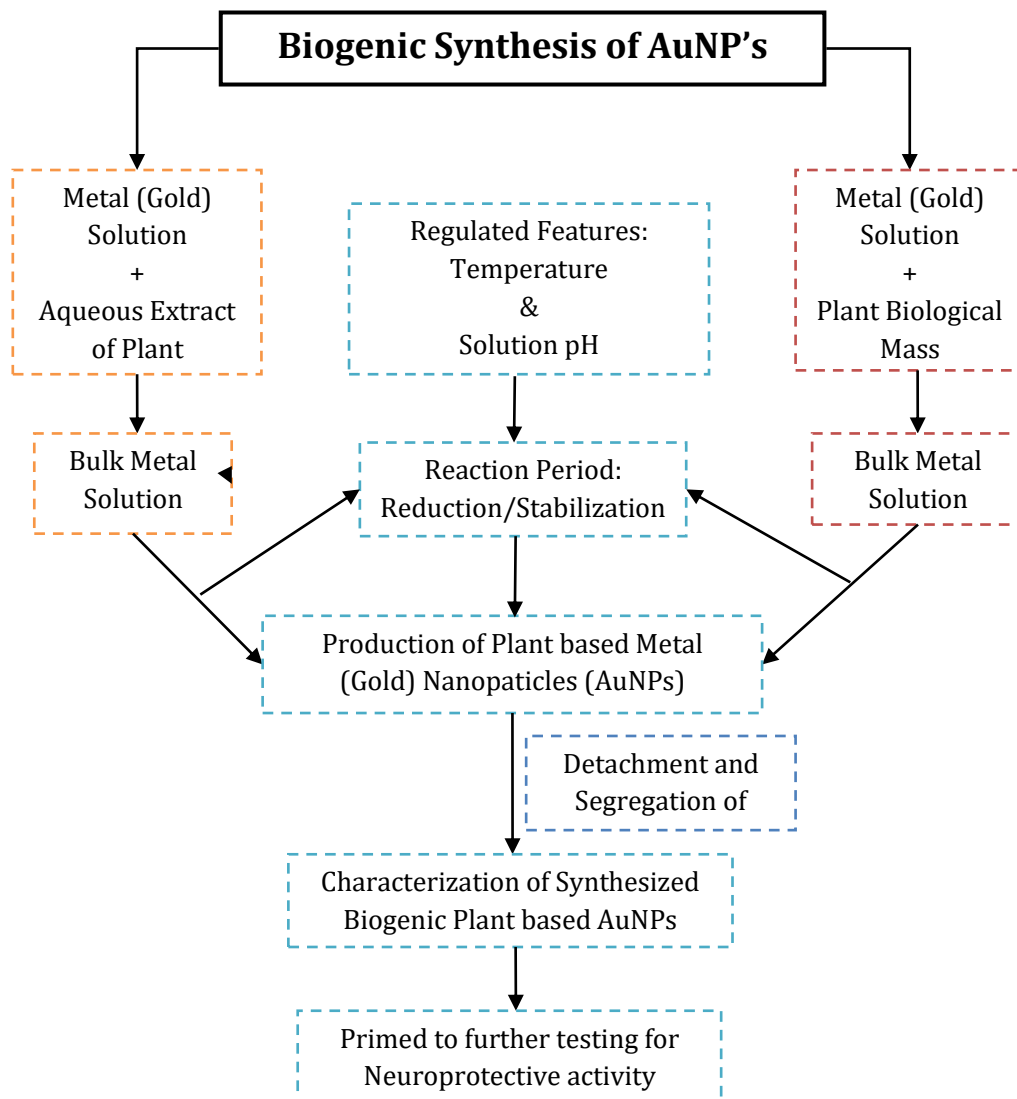


Figure No. 1: General synthetic procedure steps in production of plant based gold nanoparticles (AuNP's)[43]

3.1 Neuroprotective activity of *Terminalia arjuna* based AuNPs across BBB

Terminalia arjuna, an Asian traditional plant with immense medicinal potential. Gold nanoparticles (AuNP's) from the extracts of this plant though had not been widely studied for their therapeutic scope, however been observed to show moderate antibacterial activities[38]. In reference, to neuroprotective activity AuNPs of *Terminalia arjuna*, study by Suganthi & Co., in year 2018 suggested their anticholinesterases, antiamyloidogenic and antioxidant activity *in vitro*[44].

3.1.1 Biogenic synthesis of AuNPs using bark extract of *Terminalia arjuna*

- Crude sample *T. arjuna* wash it in running water & sterilized using ethanol.
- Dry and finely powdered.
- 1 gm of powdered sample to be taken with 100 ml of ethanol/water to make aq. and ethanolic extract respectively.

- The above, incubate for 5-10 min. and filtered with Whatman paper and filtrate was stored at 4 degree Celsius.
- Later, for AuNPs synthesis treat 10 ml of aliquot of the extract with 1 mM HAuCl₄.
- The reaction mixture is then well stirred for 15 min. at 80 degree Celsius.
- Visualized for colour change to the mixture.
- For bimetallic nanoparticles 0.01 M HAuCl₄ mixed with 10 ml of extract, stirred at room temperature for 1 min. to get AuNPs. Later, the colloidal solution is added with 0.01 M PdCl₂ stirred for 60 min. at normal room temp. to get Au/Pd bimetallic nanoparticles.
- Later they obtained AuNPs are calcinated, refined and stored in air gripped container.

3.1.2 Characterization of synthesized AuNPs using bark extract of *Terminalia arjuna*

The characterization of synthesized AuNPs is done via variety of modern analytical and spectroscopic techniques.

- UV-VIS Spectroscopy: Suggests Surface Plasmon resonance absorption of AuNPs at wavelength of

- 536 nm. Similarly, FTIR, HRTEM and EDX techniques are also used for accurate evaluation and characterization of synthesized AuNPs.
- FESEM, TEM & XRD are used to reveal the shape formation of AuNPs such as spherical, triangular etc along with sizes ranging from 20 & 50 nm.
- Techniques like DLS and ZP (zeta potential) suggest the average sizes of AuNPs.

3.1.3 Brain targeting through synthesized *Terminalia arjuna* extract AuNPs across BBB

Synthesized AuNPs in research by **Suganthi et al.**, has shown remarkable neuroprotective effects against Alzheimer's disease (AD), a neurological health issue amongst old age individuals, which has seen an exponential rise in recent years and a major cause of dementia, leading to reduction of both mental & physical activities and cognitive skills in day to day life[44].

The result from the studies suggested AuNPs synthesized from both aqueous and ethanolic extract of *Terminalia arjuna*, when compared to the standard of Donepezil drug (Conventional antiAChE/BuChE inhibitor) possessed better Acetylcholinesterase (AChE) inhibitory activity, of 98.23 % at the same of 50 µg/ml as positive control in concentration-dependent manner. Similarly, the AuNPs also showed excellent butyrylcholinesterase (BuChE) inhibitory response of 99.4%, at 5.05 µg/ml concentration when compared with the positive control (Donepezil) at same concentration. Considering the dual AChE & BuChE inhibitory of synthesized AuNPs, they could play vital role in regulating abrupt ACh level in AD[44].

3.2. Neuroprotective activity of *Paeonia montan* based AuNPs

Paeonia montan a traditional Chinese plant bears multiple medicinal activities such as anti-allergic, anti-inflammatory etc[47]. However, its related AuNPs had rarely been studied for neuroprotective and other medicinal activity. In a unique research by Xue and Co. in 2019, AuNPs synthesized from its root extract showed efficient response against Parkinson disease & related disorders both *In-vitro* & *In-vivo* study[39].

3.2.1 Biogenic synthesis of AuNPs using root extract of *Paeonia montan*

Synthetic & characterization procedure to plant based AuNPs are mostly same or with minor changes as suggested above:

- After the mandatory process of collection, washing and fractionation of root extract, procedure to synthesis of AuNPs are conducted.
- 0.1 mM HauCl_4 (10 ml) is mixed above 10 ml of obtained ethylacetate fraction and incubated for 4 hrs at normal surrounding temperature.
- As previously suggested colour change visualization depicts the biosynthesis of gold nanoparticles

3.2.2 Characterization of synthesized AuNPs using root extract of *Paeonia montan*

- As shown earlier the characterization process is similar & utilizes variety of spectroscopic and analytical techniques suggested the adequate sizes of AuNPs to cross BBB.

3.2.3 Neuroprotective activity of *Paeonia montan* AuNPs across BBB

The Synthesized AuNPs as results shown by **Xue et al.**, suggested that they efficiently regulated the nitric oxide

release *in vitro* (cultured cell lines murine microglial BV2), suggesting nil to minimal cell based toxicity even at higher concentration of doses, nitric oxide balance status is vital for brain cell protective effects, on contrary aberrant levels might lead to cytotoxic & detrimental effects. Moreover, the Synthesized AuNPs not only down regulate the levels of inflammatory cytokines but also effectively scavenges the reactive oxygen species (ROS). Additionally, activity observed *in vivo*, the synthesized AuNPs were observed to prevent dopaminergic neuro-inflammation via up regulating the neurotransmitters dopamine level in mice with pre-induced Parkinson[37].

3.3 Neuroprotective effects of Plant *Ephedra sinica* (ES) Stapf extract AuNPs

Ephedra sinica a Chinese plant species though not widely assessed for its medicinal value but in past its extract had been witnessed to show anti-angiogenic, anticancer and anti-invasive activity[46]. In respect to extract based AuNPs of this plant no major assessment of biological activity has been studied. However, the extract based AuNPs from *Ephedra sinica* has been found to treat Chronic neuro-inflammation in microglia cells induced through neurodegenerative diseases, Microglia is been termed as the major and initial immune defence system in CNS comprising 10-15% of all cells[36].

3.3.1 Biogenic synthesis of AuNPs using root extract of *Ephedra sinica* Stapf (ES)

- After the mandatory process of collection, washing and fractionation of ES stem extract, procedure to synthesis of AuNPs are conducted.
- 1 mM HauCl_4 solution is mixed with above attained 2mg/ml ES extract with rigorous stirring, upon stirring it shows violet colour and later is incubated for 10 min at normal surrounding temperature (22-25 degree Celsius).
- Later, to remove residue, the mixture is centrifuged at 13000 RPM for 20 min. and synthesized AuNPs are further moved to characterization.
- As previously suggested colour change visualization depicts the biosynthesis of gold nanoparticles.

3.3.2 Characterization of synthesized AuNPs using stem extract of *Ephedra sinica* Stapf (ES)

- As shown earlier the characterization process is similar & utilizes variety of spectroscopic and analytical techniques suggested the adequate sizes of AuNPs to cross BBB.

3.3.3 Neuroprotective activity of *Ephedra sinica Stapf* (ES) AuNPs across BBB

As studied by Park *et al.*, synthesized AuNPs of *Ephedra sinica Stapf* (ES) has been witnessed to exhibit anti neuroinflammatory abilities in lipopolysaccharide triggered microglia. Additionally, it also decreases ROS levels along with down regulation of inflammation causing cytokines and related mediators, suppressing the impact of neurodegenerative disorder. Moreover, the synthesized AuNP has been observed to affect multiple cell based signalling pathways in lipopolysaccharide triggered microglia which leads to down regulation of variety of aberrantly disturbed

JAK/STAT, ERK-1/2, NF- κ B, IKK- α/β , p38 and MAPK and JNK pathways. However, this also leads to increase in expression of Heme Oxygenase (HO)-1 & NADPH Quinone Dehydrogenase-1 gene and induction Nrf2 and AMPK in microglia CNS. Considering the remarkable ability of ES-AuNPs, could lead to an smart therapeutic strategy for treating cerebral disorders[36].

4. Conclusion

The current review here suggests the scope of potential plant based gold nanoparticles for targeted/neuroprotective drug delivery to the brain, enduring a vital new generation steadfast therapeutic strategy for neurodegenerative disorders. Considering the fact to, rising numbers of suspected brain disorders and the limitations to currently in place conventional neurology medications, there is an immediate need to explore alternatives but scientifically vibrant treatment option as this, which not only offers the great flexibility to overcome multiple biological, physical and chemical complexity within the brain system but also could lay the foundation to conventional site specific brain targeting therapy across BBB. Plants based AuNPs as suggested in the review, later, could be functionalized to bind with multiple numbers of neurological drugs/monoclonal antibodies, transferrin etc to cross BBB & identifying simultaneous pointed molecular targets for treatment such as in brain tumours. Due to macro level sizes of Plant-AuNPs, this approach is rather, could be critical to targeted drug delivery in across the brain and offers no detrimental impact on normal's cells surrounding the targeted diseased area like in brain cancer. Hence, synthesis and utilization of Plant-AuNPs could be a consequential means, not only to explore and adopt green synthesis protocols for multiple numbers of cerebral diseases like Parkinsons, Alzheimer's, Brain tumors/cancer, Schizophrenia etc. but also could revolutionize advancements in neurological therapies. However, such drastic interventions could be time taking and requires multiple phases of meticulous clinical studies before it's recommended for use. Therefore, confirmations to AuNPs biological activity along with optimal dosage, usage, administration profile etc are very much desirable through well designed clinical trial.

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