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Clinical Translation of Gold Nanoparticles into Effective Neuromedicines: Bottlenecks & Future Prospects

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ABSTRACT: Nanotechnology is the most interesting and advance area of research field in the current date. Nanoparticles are defined as a substance whose particle size varies between 1-100nm.This review focus on the potential of gold nanoparticles to be used as an alternative to available neuromedicines due to their various unique properties. This paper also deals with advantages of gold nanoparticles over available neuromedicines along with various bottlenecks in the translation of gold nanoparticles into effective neuromedicines and the future perspective or scope of gold nanoparticles to be used as neuromedicines.

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INTRODUCTION

Due to the increase in stress, unhealthy lifestyle in this growing competitive world as well as prolonged ageing, has led to the increase in neurological disorders. Neurological disorders can be broadly divided in two categories (A) Neuropsychiatric category and (B) other neurological disorders categories. Disorders like Parkinson's, Alzheimer, other dementia, and multiple sclerosis, migraine and epilepsy falls under the neuropsychiatric category and diseases like cerebrovascular disease, neuroinfection, neurological injuries falls under other neurological disorders [1].

Neurological disorders can also be classified based on the age of the person

(A) Neurological disorder at early age – which includes Autism, Cerebral palsy, Tourette syndrome.

(B) Neurological disorder at any age- Migraine, Epilepsy, Multiple sclerosis, Traumatic brain injury, Spinal cord injury.

(C) Neurological disorder at later age-Alzheimer, Parkinson's disease. There are many other diseases or disorders to but these are the most common disorders that are responsible for neurological morbidity and mortality [2].

Till date there are not effective therapies available for many of the neurological disorders. We all know neurons can't be regenerated which means the number of neurons at the time of birth till old age remains same and this is the reason why the neurons once damaged cannot be regenerated it can only be treated. Firstly for the use of nanotechnology in nanomedicine we need to first check the safety and toxicological effects of the nanomedicine. Neuromedicines are considered as an alternate for the treatment of neurological diseases but is not effective there are some issues related to use of neuromedicines i.e. safety and toxicity issue, it may cross blood brain barrier, can trigger different process for blood coagulation other effect may be since there particle size is very small they can be hazardous to respiratory system as well [3].

Biotechnology and Biomedical field widely uses gold nanoparticles due to the fact that it has large surface area and high electron conductivity [4]. They are proven to be the safest and less toxic agents for the drug delivery system

compared to the other neuromedicines [5]. Property like biocompatibility, nontoxicity, good physical, chemical and photo properties of gold and their structural design which enables us to coat the surface of gold nanoparticles with various target signals have provided it to be the used as an effective nanomedicine for treatment of neurodisorders[6][7][8].

ISSUES AND DRAWBACKS OF AVAILABLE NEUROMEDICINES

Neuromedicines are the special class of drugs that are used in the treatment of neurological disorders e.g. - Parkinson, Alzheimer's, epilepsy, multiple sclerosis etc. Some e.g. of neuromedicines are :- Levetiracetam, lamotrigine, and Phenobarbital used in the treatment of the disease Alzheimer and epilepsy [9] other drugs such as interferon β (Avonex, Betaseron, Extavia, plegredy), Glatiramer Acetate (Copaxone, Glatope), Fingolimod (Gilenya), Triflunomide (Aubagio), Dimethyl Fumarate (tecfidera), Alemtuzumab (Lemtrada), Natalizumab (Tysabri), Ocrelizumab (Ocrevus), Mitoxantrone (Novantrone), are some of the drugs for the treatment of multiple sclerosis [10] [11] [12]. The neurodrugs classes such as Carbidopa-levodopa (Lodosyn) [13] [14], anticholinergics benzatropin (cogentin) [15] [16], Catechol O-methyl transferase (COMT) inhibitors (comtan) [17] [18], Dopamine agonists (levodopa, requip, epokin) [19] [20] [21] and Mao-β inhibitors (Eldepryl, Zelapar) [22] [23] are used in the Parkinson disease. All these neuromedicines which are used in the treatment have many drawback and toxic effects on human body. One of the major drawback of these neuromedicines are they are unable to cross blood brain barrier and are not the permanent cure. These drugs have many toxic effects like Levetiracetam is toxic to our body and can lead to respiratory depression [24]. Lamotrigine has symptoms of fatigue, sedation, confusion [25]. Interferon-β drugs have side effects such as headache flue like symptoms, seizures, Liver problems, feeling of suicide and depression. Glatiramer Acetate have a side effect like shortness of breath, chest pain etc., Fingolimod has side effects such as Diarrhea, Back pain, Liver problems, Sinus infections, Abdominal pain. Triflunomide drug has an effect like thinning of hair, Nausea, Diarrhea. Alemtuzumabhas have side effects such as Headache, Rash, Nausea, and Fever & Natalizunabhas have side effects like joint pain, fever, feeling sick or tired and dizziness. Ocrelizumab drug is not prescribed to person who is suffering from hepatitis B because it can react with other drug and cause symptoms like itchy skin, rash, throat irritation another and the less prescribed class of drug is Mitoxantrone drug which has most severe side effect and can be fatal too. Doctors usually prescribe this only if multiple sclerosis is growing worse quickly and if other drugs haven't helped. It can seriously affect your heart and may make you more likely to get blood cancer [10] [11] [12]. These are some drugs used as a neuromedicines in the field of neurosciences to cure neuro diseases but have drawbacks as well. There future research can be based of increasing their efficiency by attaching these drugs to particle which can enhance their permeability across the blood brain barrier, increase their accuracy, and reduce their toxicity. The specificity and permeability has the main role in designing of any medicine as the drug needs to be delivered to the specific target though different biological barriers present.

FEATURES OF EFFECTIVE NEUROMEDICINES

Any drug which needs to be qualified as an orally administered pharmaceutical product need to have certain basic properties and if the drug needs to be effective it needs to have other properties too which will enhance the activity of the drug.

The Basic properties that a drug need to have was first discovered by Christopher A. Lipinski in 1997 he named the law as Lipinski rule of 5 (RO5) i.e. drugs need to have

A. It should have Octanol-water partition coefficient log *P* not greater than 3.
B. It should have molecular mass less than 300 Daltons.
C. It should have not more than 3 hydrogen bond donors.
D. It should not have not more than 3 hydrogen bond acceptors
E. It should not have more than 3 rotatable bonds.

So, if a neuromedicines is to be designed which needs to be administered orally needs to follow Lipinski rule of 5 [26] along with other properties these properties are need to be taken care as they are irrespective of the fact that they have to be taken orally. These properties are applicable for all the neuromedicines as these will enhance the activity of the drug. The other property includes Size, shape, specificity (target), ligand attached, stability, toxicity, and permeability (**Table 1**) [27-41].

Table 1. Represents properties and their function of an effective neuromedicines [27-41]

Properties	Function
Size	Developing neuromedicines should have a size less than 200nm to cross blood brain barrier.
Shape	Transportation of particle is affected shape related factors i.e. aspect ratio, edge geometry which control the cell particle interaction and alters drug release kinetics. E.g. nano rods, Nanosphere, hollow Nanosphere, icosahedra etc.
Specificity	They medicine designed should be specific for target. For neuromedicines target can be central nervous system, peripheral nervous system, neurotransmitters, specific proteins or receptor in neuron, and an enzyme.

Ligand	The ligand can be present or not. Ligand can help in the interaction of the medicine/drug/chemical molecule to the target also helps in blood circulation, protein adsorption and can increase hydrophobicity.
Charge	Charge can be due to the molecule itself or due to the ligands attach and charge on particle determines the efficiency of the medicine for e.g. - for intravenous application negative charged compound or particles are preferred.
Stability	Stability is an important factor because even if the composition or compound is formed if the final compound that is to be used is not stable in-vivo the development of the medicine is useless.
Toxicity	Toxicity is an important and an essential factor development of a drug. Medicine should not be toxic to the targeted organ or other organs and should not produce side effects.
Permeability	Permeability is an important factor as drug administered needs to overcome a biological barrier present inside the body of an organism. In case of neuromedicines permeability is an important factor as the drug administered if target's the central nervous system needs to cross blood brain barrier.

GOLD NANOPARTICLES POTENTIAL AS NEUROMEDICINES

Due to the small size and increase in permeability of nanoparticles they can be used an essential tool for the transportation of drug not only in other parts of the body but to the brain too as they have an ability to cross blood brain barrier [42][43] [44] [45]. Also, when administered into the blood nanoparticles increases the binding property of the drug to its receptor on the endothelial cells which lines the blood brain barrier while circulating and will help in administering the drug across the barrier [46][47][48][49]. In the last few years many advances have been made in nano systems for the delivery of drug in the CNS e.g. polymorphic nanoparticles and micelles, dendrimers, liposome and solid lipid nanoparticles. Even if they (nanoparticles) can cross the endothelial cells it was seen only few amount of drug was delivered in the drug when the particle crossed blood brain barrier [50] [51] [52]. Hopefully, till now gold nanoparticles appears to be an effective tool to transport drug across the blood brain barrier affectively over other nanoparticles. Various studies have been conducted which suggest contrary results like one study suggested that best cellular uptake size to be around 50nm [53] [54] [55] [56] whereas another study suggest 20nm size to be the better size. This type of conclusion can be due to administration of gold nanoparticles with drug on different cell lines. [53][57].Our topic is based on the uptake of gold nanoparticles in brain via blood brain barrier [58] [59]. US have filed some patent which show uptake of gold nanoparticles (US 20110111040 and US 20110262546A1) [60].

On 2008 colloidal forms gold nanoparticles of different sizes were administered intravenously into mice [61].Result showed that they were able to observe that gold nanoparticles have the ability to pass through the blood brain barrier and this passage mainly depends upon the size of the gold nanoparticles. The results were as follows the particle which had size approx. 15nm showed 100 times better ability to penetrate than the 100nm particle.

Then in 2012 the experiment was performed in which impact of charge and size on gold nanoparticles was observed to see the accumulation of particle in various organs [62]. Gold particle bearing positive and negative charge were used of different sizes ranging from 1.4nm-200nm out of which 18nm particle showed maximum accumulation in CNS and greatest penetration was observed by negatively charged particles. Interestingly shilo et al. used barbiturate coated gold nanoparticles on cell type bEnd.3 (brain endothelial cells) in-vitro and he suggested 70nm size gold nanoparticles to be appropriate for drug delivery in brain [58].For a gold nanoparticles to be effective in a field of medical science the drug that is to be administered of 20nm size should be attached to it by this way we can administer blood brain barrier impermeable drug to the brain and also can be used for diagnosis. Cheng and his team [62] showed that Trans activator of transcription (TAT) peptide was used to modify the gold nanoparticles surface were used in efficient transfer of tumor drug named doxorubicin and an agent gadolinium to CNS. Doxorubicin is an impermeable drug towards blood brain barrier, but when attached to gold nanoparticles and TAT it showed increase in survival rate of intracranial glioma mice. It was also used to administer gadolinium which helps in developing contrast of the brain for MRI. Other studies showed that molecules like glucose [63], horse reddish peroxidase can also be transferred to brain via gold nanoparticles [64]. Sela and his team [59] demonstrated the relation between ions and activity of the gold nanoparticles. They injected ions (K^+, NA^+ and Ca^{2+}) channel blockers and after some time they saw the 50% decrease in amount of gold nanoparticles in CNS. It clearly depicts that if the iconic balance it disturbed the permeability of gold nanoparticles to blood brain barrier decreases [65] [66]. Ion channel blockers could control the Migration of gold nanoparticles via blood brain barrier [67]. Some facts that needs to be investigated about the ion channel blockers that weather they control the ion channel of all the body or only the brain's and what will be their blockade that will prevent gold nanoparticles from entering other organs [59].

Recent study also shows that gold nanoparticles are used as a tool against Neurological Bacterial infections. As normal drug cannot pass through blood brain barrier so the major challenge of making the drug is to check its permeability

against the blood brain barrier. [68] [69]. **Fig.1.** shows the application of gold nanoparticles in treatment of central nervous system (CNS) infections.

One of the main reasons for development of gold nanoparticles against bacterial infection was the increasing amount of bacterial resistance. So, the gold nanoparticles seems to be the perfect tool in tackling neurological bacterial infection because they can cross the blood brain barrier easily as discussed earlier.

There are several literatures that show the antibacterial activity by gold nanoparticles against neurological bacterial infection [70] e.g. - Gold nanoparticles antibacterial activity against S. *pneumonia* was carried out by Ortiz-bentiez et al [71]. Another study by Chandran et al showed the efficacy of herbally synthesized gold nanoparticles with that of Escherichia *coli* and Listeria *monocytogens* species [72].

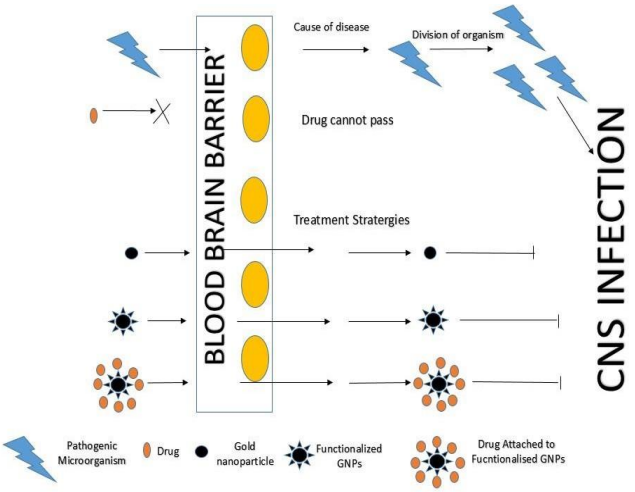

Fig.1. Application of gold nanoparticles in treatment of central nervous system (CNS) infections.

ADVANTAGES OF GOLD NANOPARTICLES OVER AVAILABLE NEUROMEDICINES

There are many advantages of gold nanoparticles over other neuromedicines. One of the biggest advantage is that it is used as a drug delivery tool because of their biological compatibility over other medicines, their relative stability while formation of a full complex, their ease of functionalization, binding capacity to variety of functional groups, ability to be trace by CT imaging and the most peculiar feature that make them effective and efficient over other available neuromedicines is the size modulation [58][59][46][73][74][75].

Small size of the nanoparticles can be used to deliver the drug across the blood brain barrier as other neuromedicines (doxorubicin, Levetiracetam, lamotrigine, Phenobarbital) / drug used in treatment of neuro diseases like Alzheimer and epilepsy don't have that potential to cross the blood brain barrier e.g. of one such drug is doxorubicin this drug is impermeable but when attached to gold nanoparticles can be made permeable across the blood brain barrier [62].

Other properties which gold nanoparticles includes are the Raman scattering, surface plasmon resonance, non- linear optical properties and quantized charging effect [76].Neuromedicines don't have enough permeability and lack specificity of the target the whereas when the drug is administered along with gold nanoparticles the specificity of the drug increases and due to that small size of the particle permeability also increases after the administration visualization can also be performed which cannot be performed when testing with a normal neuromedicines [58] [59] [62] [68] [69]. Gold nanoparticles (GNPs) have been used very much as a cancer antigen in many therapies and have many advantages over other non materials and available neuromedicines [77].GNPs have high surface area which provides the ability to bind to many functional groups that helps in drug loading and increases the permeability of the drug against different physiological barriers mainly blood brain barrier if the particle is used as a neuromedicines [78].These GNPs are biocompatible and can be used in conjugation with many proteins, DNA, enzymes and biomolecules [79]. Their accuracy is due to controlled dispersity and small size which allow them to easily target the specific site [80]. They are also non cytotoxic to other cells and can be easily synthesized [81] unlike the other drug name Levetiracetam which has been found in potential neuromedicines in case of Alzheimer disease is toxic to our body and can lead to respiratory depression [24].Another drug lamotrigine which is been used for epilepsy patients have been found toxic and patient administered with that drug shows the symptom of fatigue, sedation, confusion etc. [25]

BOTTLENECKS IN THE TRANSLATION OF GOLD NANOPARTICLES INTO EFFECTIVE NEUROMEDICINES

Gold nanoparticles have many advantages to them but the synthesis of gold nanoparticles into effective neuromedicines may have some bottlenecks. Firstly the particle which is gold in case of gold nanoparticles should be attached to some ligand or group that have good permeability and should be degradable i.e. it should not accumulate inside the body as scene in mice as accumulation can lead to toxicities and other health related issues[82].

Another reason in the translation of gold nanoparticles is with the use of CTAB synthetic chemical which is very important in production of different shapes of nano gold particles because it is toxic to cells on its own at micro molar concentration [83] also it is noted that binding with CTAB makes nanoparticles surface less available as compared to nanoparticles made without CTAB which might affect the actual dose of the particle [83].

During the synthesis of gold particle many impurities can be found the main ingredient is Au^0 and the impurities may include Au^{3+}other impurity present depends upon the type of

method used in generation of gold nano particles for e.g.: - In case of citrate nano gold particle the impurity present are Au^{3+} and tri sodium citrate. These impurities are cytotoxic to the cells; evidence shows the accumulation of impurities in the liver and relative side effects of gold nanoparticles based nano system [84]. Hana et al. discovered the toxic effect of positively charged goldnanoparticle in *C. elegans* [85].

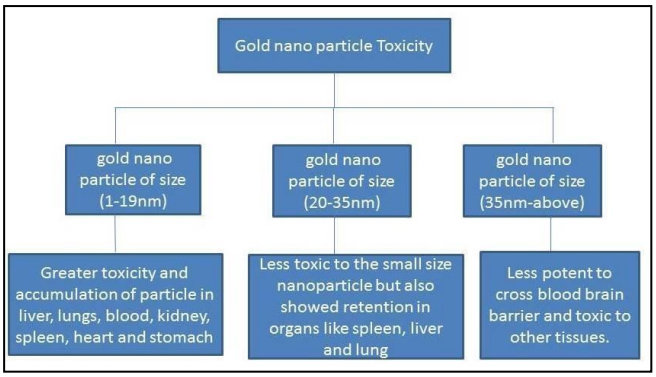

Fig 2. Flow chart detecting the drawback of gold nanoparticles when used as a neuromedicines will not only affect brain but other organs as well [86][87][88][89][90][91].

Other than toxicity, size and distribution are also the major factor that needs to be taken into consideration (**Fig 2**). Tang et al showed that gold nanoparticles of smaller size (8nm) showed increase in liver toxicity when coated with glutathione (reduced) as compared to larger size gold particle (32nm) [86].

It has also been seen that higher accumulation of gold nanoparticles in case of rat when compared to that of mice predicts that physiology of the organism also depicts the level of toxicity as to much difference in toxicity has been seen in closely related species. It has also been observed that gold particles mainly accumulated in tissue like spleen, lung and liver and those particles whose size were 15nm accumulated in blood, liver, spleen, kidney, brain, lung, heart and stomach etc [91]. Additionally, scientist found that retention time for gold nanoparticles inside the body of an organism is very long which may be harmful for the organism [90]. For a nanoparticles/drug to be used as a neuromedicines/medicine respectively the needs to have qualify all the aspects listed below.

Technical aspect for a gold nanomedicine is one of the main drawback for its production to neuromedicines as the gold nanoparticles can cross the blood brain barrier due to their small size but can also be toxic to the brain and also it has been seen that it gets accumulated in the liver of the mice and can be toxic not only to the brain but to the other organs as well (**Fig 3**).

The most important of the described drawback of the gold nanoparticles is the clinical aspects since the drug has to made for the consumption of humans the clinical trial in human has to be done and the effectiveness of the drug against the disease patients has to be checked. Till now very few clinical trial for gold nanoparticles as a neuro medicine have been conducted another bottle neck lies in the production the gold nanoparticles since it uses the gold as an important component due to its various advantageous properties the effective coast of making the neuromedicines will be high and not every person will be able to afford it so the economical aspect remains one the drawback in production of gold nanoparticles as a neuromedicines.

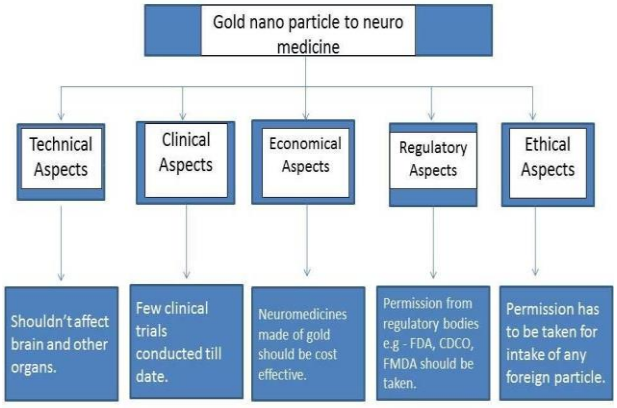

Fig 3. Different aspects required by gold nanoparticles to qualify as neuromedicines and their drawbacks

Any drug which has to be released has to get permission from different regulatory bodies present in the country e.g. FDA, CDCO, FMDA etc. FDA has only approved only few nano-based technology only for the purpose of diagnostics [92] [93]. Second major drawback after the clinical trial is the ethical issues faced by gold nanoparticles many countries won't allow the use of gold nanoparticles as a neuromedicines for human as intake/injection of any foreign particle to human is not under the ethics. Mentioned above aspects were major drawbacks that the gold nanoparticle as a neuromedicines has to face or is facing in the present situation.

FUTURE PROSPECTS

To overcome the toxicity many other groups will be attached in surface of gold particles that will not only help in reducing the toxicity but will help in effective transfer, anchoring of the drug. The groups such as thiolate [94] [95] [96], dithiolate [97], dithiocarbamate [98], amine [99], carboxylate [99], isothiocyanate [99] [95] moieties are used as an anchoring tool and for reduction of toxicity. Suggestion from recent literatures have also been made which tells that direct Au(gold)-C(carbon) bond formation can be achieved by the help of trimethyl tin leaving group however the nanoparticles have not been efficiently tested [100]. Gold nanoparticles are used widely in field of nanotechnology for development of neuromedicines due to the inherent low toxicity of gold. Caution to the present scenario is that some gold nanoparticles may be toxic based on their coating and size. Clinical trials have been going on and [101].

CONCLUSION

We will be able to see the more of gold nanoparticles in future as they will not only help in curing of the diseases but will also play an important factor in detection of diseases or providing high contrast imaging of blood vessels organ etc. Since blood brain barrier permeability has been achieved by the gold nanoparticles and also it have been seen that the proper delivery of lexicans by permeability of nanoparticles to CNS has been achieved. Hope this nanotechnology will be able to cure neurodegenerative disorders and also our drug delivery system will improve a lot.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

As a review paper we confirm that any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies.

CONSENT FOR PUBLICATION

Written consent to publish potentially identifying information, such as details, or photographs, was obtained from journals.

AVAILABILITY OF DATA AND MATERIAL

All the data and materials are taken from the referencing journals.

CONFLICTS OF INTEREST

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All those designated authors should meet all the criteria for authorship. We attest that all authors contributed significantly to the creation of this manuscript. We confirm that manuscript has been read and approved by all named authors. We confirm that order of authors listed in the manuscript has been approved by all named authors.

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