THE GREEN SYNTHESIS OF CERIUM OXIDE AND OTHER METAL NANOPARTICLES: FOCUS ON BIOLOGICAL APPLICATIONS IN ALZHEIMER DISEASE TREATMENT

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ABSTRACT :

Metal nanoparticles have been used as drug delivery agents in the area of medicine for decades. Green metal nanoparticles, on the other hand, have grown in popularity in recent years due to their environmental friendliness. Furthermore, unlike chemical production of nanoparticles, their creation does not need a large amount of energy. Metal nanoparticles come in a variety of sizes and shapes. However, their use in drug delivery is contingent on the characteristics of the resultant nanoparticles. Antioxidant and anti-inflammatory treatments have been studied either alone or in conjunction with already available medications. However, little progress has been made since the majority of chemicals do not penetrate the blood-brain barrier. Green synthesis of nanoparticles, which is a component of

nanotechnology, will emerge as a novel drug delivery carrier in a variety of treatments. Because of their beneficial uses as catalysts, fuel cells, and antioxidants in biological systems, they have gained a lot of interest in nanotechnology. Green Synthesis Nanoparticles' unique capacity to modify its oxidation state between +3 and +4 makes it a viable therapeutic option for many disorders related with oxidative stress and inflammation, as well as a robust drug delivery vehicle. Furthermore, the existence of a mixed valance state is critical for scavenging reactive oxygen and nitrogen species.

Keywords:

Metal Nanoparticles, Chemical Synthesis, Drug Delivery agents, Environmentally friendly, Green Synthesis.

1.Introduction :

Green synthesis of nanoparticles drug delivery is indeed a promising new medical concept that intends to combine environmentally friendly approaches with effective drug systems to ensure that therapeutic components reach the body effectively.The desire to create a unique method of medicine distribution was motivated by issues with current drug delivery methods. For a long time, the use of compounds such as syrups, pills, capsules, and other solutions was plagued by a variety of issues. Variations in plasma levels, first-pass metabolism, and decreased efficacy were among the concerns observed. The notion of nanotechnology is centred on the use of small, physiologically compatible synthetic materials to enhance medicine delivery. The compact size raises the surface area to volume ratio significantly. Furthermore, since they are physiologically friendly, They have no negative effects on the body and are appropriately absorbed. Furthermore, the particles should not be harmful to the environment. The paper that follows offers an overview of green nanoparticle production and how the particles might be used to deliver drugs therapeutically[1,2].

2.Green Synthesis of Nanoparticles :

Prior to the discovery of green synthesis nanoparticles, the particles were often created using chemicals. However, as public awareness of the need of environmental conservation rose, eco-friendly conservation methods were created. The term "green" is now frequently used in a range of fields to refer to practises that have no or little negative environmental effect. According to Kanwar, Rathee, Salunke, and Mehta [2019][1] previous processes often used chemicals to stabilise the resulting particles and prevent them from clustering. The discovery that organic molecules may be used in the production of nanoparticles has led in the creation of more ecologically friendly technology. According to Shabir Ahmad et al. [2019][2] the manufacture of silver-based nanoparticles has lately included the utilisation of biological methods that involve reducing agents such as bacteria, fungus, and plants to prevent the particles from aggregating.

3. Synthesis of Metal Nanoparticles :

Metal nanoparticles may be produced by a number of methods. The techniques are primarily governed by the metal's characteristics. Furthermore, some are favoured over others since they are less costly to produce and have a variety of medical uses (Raj, Ingle, Birla, Yadav, & Santosh,

2015)[3] Here are several metal nanoparticles that scientists often develop and used.

3.1Magnetite nanoparticles :

According to Iravani (2011)[4], Fe2O3 nanoparticles were created in a study utilising alfafa with a pH of 10, and the resulting particles varied in size from 1-4nm. When the pH was decreased, however, a substantial number of particles were formed. Yew et al. (2016)[5] used the same process to make Fe3O4 nanoparticles using K. alvarezzi as an organic reducing agent. K. alvarezzi was fed Fe3+ and Fe2+ during the experiment, and the pH was maintained at 11 using a NaOH solution. A magnet was used to separate the metal nanoparticles from each other.

3.2 Silver nanoparticles :

The most current approach for creating silver nanoparticles, according to Zaina and Shamaa (2014)[6] is the reduction of silver salts. Toxic metals were used as reducing agents in previous approaches. Green alternatives have been created, however, owing to the harmful environmental impacts of these compounds (Ahmed, Babu, Swami, & Ikram, 2016)[7] In the publication "Green Synthesis of Silver Nanoparticles utilizing Latex of Jatropha Curcas," by Bar, Bhui, Sahoo, Sarkar, and Misra (2009), silver nitrate may be used as a biological reducing agent in the manufacture of nanoparticles[8].

3.3 Copper nanoparticles :

That according Shende, Ingle, Gade, and Rai, copper nanoparticles have become more popular in recent years because of their lower cost (2015). CuSO4.5H2O and C. medica juice were extracted and then heated to between 60 and 100 degrees Celsius (Nagaonkar, Shende, & Rai, 2015)[9] Because the procedure is less complicated and uses less chemicals, it is affordably priced (Singh, Kim, Zhang, & Yang, 2016)[10] Aditionally , the approach is entirely organic and environmentally benign.

3.4 Zinc nanoparticles :

Antimicrobial and wound-healing properties of zinc oxide nanoparticles However, owing to the toxicity of the chemicals utilised as reducing agents in previous techniques, production is now

confined to plants and microorganisms (Agarwal, Kumar, & Rajeshkumar, 2017)[11] Zinc nanoparticles can be synthesised efficiently using zinc nitrate (Hirematha & Antonyraj, 2013)[12]. Additionally, Sangeetha, Rajeshwari, and Venckatesh (2011)[13] report on the effective usage of Aloe vera extract as a reducing agent.

3.5 Gold nanoparticles :

Gold nanoparticles are often synthesised by reacting gold chloride with a variety of biological reductants (Aromal & Philip, 2012).[14] According to Kumar, Gokavarapu, Kapadia, and Roy (2011)[15] Cassia auriculata extract is one of the chemicals used. However, due to the expensive cost of the raw material and the relatively large size of the nanoparticles formed, gold nanoparticles are not usually favoured (Elia, et al., 2014)[16] Additionally, gold lacks major medical properties that would justify its extensive production.

3.6 Cerium oxide nanoparticles

It is possible to make nanoparticles in a variety of ways, both physically and chemically. The use of hazardous solvents, high temperatures, and high pressure are required for both techniques, posing a harm to the environment.[21,22] In addition, they are more expensive, require a lot of time and effort to prepare, are less biocompatible, unstable, and have a poor yield. Nanostructures with the ability to tackle these issues are becoming more important. At this time, researchers are relying on the green technique to address all of these issues. When making eco-friendly nanopowders, plants, microorganisms, or other biological products were used as reducing and/or stabilising agents.[25] It is possible to make CeO2 NPs using physical, chemical and biological processes. Because of their safety and biocompatibility, these materials are widely used in a variety of biomedical, pharmaceutical, and food-related fields. Furthermore, greener methods may offer large yields, long-term stability, and improved morphologies.[26]

4.Toxic Reducing Agents :

According to Kanwar et al. (2019), one of the key obstacles of generating green nanoparticles was the usage of non-toxic chemicals. Initially, formaldehyde and other compounds were utilised. However, novel methods for generating ecologically acceptable silver-based

nanoparticles have been identified, using reducing agents such as citrate, ascorbic acid, tyrosine, and rhubarb. The employment of non-toxic reducing chemicals, on the other hand, was seen as just the beginning of the process of creating green nanoparticles. It was necessary to verify that both the procedures used and the completed products were ecologically friendly. Traditional techniques, such as organometallic production, were not, for example, associated with hazardous chemicals. However, because to the high quantities of energy required in such treatments, they were not environmentally friendly[17].

5.Plant extracts :

One of the ecologically beneficial ways with the use of plant extracts with in manufacture of nanoparticles. Plants are selected for their greater reducing capacity and stability. Flavonoids, sucrose, hydroxylamine, and carboxyl-based compounds, and also steroids, terpenoids, and phenolic derivatives, all influence to synthesis.As according Shabir Ahmad et al. (2019), studies have demonstrated that phenolic derivatives present in oleic acid work as efficient reductants in the synthesis of silver nanoparticles. Moreover, rubber extracts, lemongrass, and starch also play a function in the decrease of silver during the manufacture of nanoparticles[18,19].

6.Bacterial synthesis :

Apart from plants, considerable interest has been shown in the use of microorganisms to synthesise nanoparticles. However, Shabir Ahmad et al. (2019) assert that the use of microorganisms often raises the risk of culture contamination. Furthermore, the method is often time-consuming and arduous, and the size of the nanoparticles generated is difficult to estimate. Other bacterial species, on the other hand, have been successfully used in particle manufacture. Bacillus subtillus and Rhodococcus sp. are two instances given by Shabir Ahmad et al (2019). Bacterial synthesis is divided into many divisions depending on the strain used[20].

7.Algae Synthesis :

Algae are primarily aquatic animals, and a variety of species have been used in the production of silver-based nanoparticles. Planktons and Rhodophyta are both exploited organisms. Although the size of algae varies significantly, this was not a factor in choosing the organism to employ in green synthesis. Isochrysis galbana and Tetraselmis gracilis are two significant species in this regard (Shabir Ahmad et al., 2019). Numerous Algae are being studied at the

moment

8. Fungi Synthesis :

When it comes to microorganisms, fungi are typically favoured over others such as bacteria since they may be grown in large quantities.Additionally, they are contaminant resistant and have a high tolerance. In essence, fungi may be cultured in a range of environments[17,22].

9. DNA Synthesis :

Recently, research has been conducted to investigate the feasibility of using DNA in the green manufacture of nanoparticles. DNA bases easily bind to silver creatin, suggesting that themolecule may be exploited, according to Shabir Ahmad et al. (2019).

10. Nanoparticles in Drug Delivery Systems :

Nanotechnology is a means of doing research that increasingly takes use of the utilisation of minute particles as well as the many ways in which the particles may be manipulated. The approach has found use in a wide range of scientific fields. However, according to Patra et al. (2018)[17], technology has benefitted the area of pharmaceutical distribution system much more than other industries. Nanotechnology is favoured in pharmaceutical administration due to its ease of manipulation, particularly when it comes to overcoming challenges connected with conventional drug delivery systems (Kumari, Ghosh, & Biswas, 2015)[18] Fast-pass metabolization, in which the drug is digested before reaching the target site, and decreased availability as a result of poor drug diffusion across membranes are two of the drawbacks (Adeyemi & Sulaiman, 2015)[19] Nanoparticles may be used for more than only sickness treatment; they can also be used in diagnostics. Particle movement throughout the body is divided into two basic modes: self-delivery and passive drug delivery.

11. Passive delivery :

The method relies on the diffusion principle, with the drug deposited into the nanoparticles through hydrophobic bonding. Because the drug concentration at the target site is lower than in

the interior of the nanoparticle, the medication will be released once it reaches the target side (Gholipourmalekabadi, Mobaraki, & Urbanska, 2017). The particle is carried to the target place via the general circulatory system as a result of temperature and pH fluctuations[10,11].

12.Self-delivery :

The medicine is absorbed into the nanoparticle and becomes a part of it in this approach. Time is essential that's because the particle may dissolve before it reaches the intended place, as per Patra et al. (2018). Antibodies and peptides, which are now present in the body, are used by self-delivery medications to carry them to their intended site of action. Therefore, the drug includes receptor for these molecules, making it easier for them to be bound and administered as a result of their presence in it[17.19].

13. Alzheimer disease DIagnosis :

Nanoparticles have been discovered to be useful in Alzheimer diagnostics, where they are steered to particular locations to offer feedback. According to Patra et al.(2018), the particles have been employed in diagnostics, where they reveal information on the location and stage of cancer. Additionally, they offer information about the disease's response to the treatment being used. Nanoparticles coated using oleic acid, for examples, have been used to detect cancer sites because of their ability to expand in size when in contact with sick cells[20] In other cases, when customised particles are combined with substances that glow in the presence of cancer, they have the ability to increase the visibility of cancerous cells. According to Kalpana and Rajeswari (2018) bioimaging is useful for more than only cancer diagnosis. Due to the fact that zinc-oxide is a very bright chemical, it may be used to diagnose a wide range of disorders. The first obstacle will be identifying the appropriate chemical that, when mixed with zinc-based nanoparticles, will provide a distinctive colour[20].

14. Delivery of Genes :

Additionally, a recent research demonstrated the ability of delivering genes to precise areas using zinc-based nanoparticles. One of the most perplexing aspects of dealing with genes is the potential of mutation degradation (Kalpana & Rajeswari, 2018). As a consequence, if nanoparticles are capable of preserving the integrity of genes while also delivering them to a precise region, they may play a critical role in gene therapy[22].

15 Conclusion :

Because of the various medicinal potential linked with the technology, the use of green production of nanoparticles in the drug delivery system has gained a lot of attention recently. Additionally, the notion of environmentally friendly, energy-efficient technology is cutting-edge[20.18]. Although nanotechnology is a relatively new idea, it has captured the medical community's interest, particularly with regard to the usage of nanoparticles. Such breakthroughs are achievable because nanoparticles are highly controllable and alleviate a large number of problems associated with traditional pharmaceutical delivery methods. Medicine, like other sciences, is directed by notions that aim to maximise resources while minimising costs. As a result, advancements in the utilisation of green approaches in the manufacture of these particles have been developed. Bacteria, fungus, plants, algae, and DNA production of nanoparticles are among the strategies employed. The particles are critical in drug delivery, where either passive or self-distribution strategies may be utilised. Furthermore, the particles are employed in the detection and diagnosis of many cancers. In essence, due to the multiple possibilities connected with the technology, green nanoparticle manufacturing and subsequent use of the particles in the area of medicine should be pursued further[20].

16. Conflict Of Interest

According to the authors, there are no known conflicts of financial or personal interest that mayhave influenced the work described here.

17.References

1. Kanwar, R., Rathee, J., Salunke, D.B. and Mehta, S.K., 2019. Green nanotechnology-driven drug delivery assemblies. *ACS omega*, *4*(5), pp.8804-8815.
2. Ahmad, S., Munir, S., Zeb, N., Ullah, A., Khan, B., Ali, J., Bilal, M., Omer, M., Alamzeb, M.Salman, S.M. and Ali, S., 2019. Green nanotechnology: A review on green synthesis of Silver nanoparticles An ecofriendly approach. *International journal of nanomedicine*,*14*,p.5087.

3. Rai, M.Ingle, A.P., Birla, S., Yadav, A. and Santos, C.A.D., 2016. Strategic role of selected noble metal nanoparticles in medicine. *Critical reviews in microbiology*, *42*(5), pp.696-719.
4. Iravani, S.,2011.Greensynthesis of metal nanoparticles using plants. *Green Chemistry*, *13*(10), pp.2638-2650.
5. Yew, Y.P., Shameli, K., Miyake, M., Kuwano, N., Khairudin, N.B.B.A., Mohamad, S.E.B. and Lee, K.X., 2016. Green synthesis of magnetite (Fe 3 O 4) nanoparticles using seaweed (Kappaphycus alvarezii) extract. *Nanoscale research letters*, *11*(1), pp.1-7.
6. Rajput, N., 2015. Methods of preparation of nanoparticles-a review. *International Journal of Advances in Engineering & Technology*, *7*(6), p.1806.
7. Bar, H. and Kr, D., 2009. Bhui, GP Sahoo, P. Sarkar, SP De, and A. Misra. *Colloids Surf., A*, *339*, pp.134-139.
8. Li, B., Wang, J., Li, J., Zhang, X., Yu, W., Wang, H., Duan, D. and Zhao, B., 2019. A comparison between continuous and batch processes to produce phosphatidylserine in the efficient and green aqueous-solid system. *Biotechnology progress*, *35*(3), p.e2777.
9. Singh, P., Kim, Y.J., Zhang, D. and Yang, D.C., 2016. Biological synthesis of nanoparticles from plants and microorganisms. *Trends in biotechnology*, *34*(7), pp.588-599.
10. Agarwal, H., Kumar, S.V. and Rajeshkumar, S., 2017. A review on green synthesis of zinc oxide nanoparticles–An eco-friendly approach. *Resource-Efficient Technologies*, *3*(4), pp.406-413.
11. Vidya, C., Hiremath, S., Chandraprabha, M.N., Antonyraj, M.L., Gopal, I.V., Jain, A. and Bansal, K., 2013. Green synthesis of ZnO nanoparticles by Calotropis gigantea. *Int J Curr Eng Technol*, *1*(1), pp.118-120.
12. Gunalan, S., Sivaraj, R. and Rajendran, V., 2012. Green synthesized ZnO nanoparticles against bacterial and fungal pathogens. *Progress in Natural Science: Materials International*, *22*(6), pp.693-700.
13. Aromal, S.A. and Philip, D., 2012. Green synthesis of gold nanoparticles using Trigonella foenum-graecum and its size-dependent catalytic activity. *Spectrochimica acta Part A: molecular and biomolecular spectroscopy*, *97*, pp.1-5.

14. Kumar, V.G., Gokavarapu, S.D., Rajeswari, A., Dhas, T.S., Karthick, V., Kapadia, Z., Shrestha, T., Barathy, I.A., Roy, A. and Sinha, S., 2011. Facile green synthesis of gold nanoparticles using leaf extract of antidiabetic potent Cassia auriculata. *Colloids and Surfaces B: Biointerfaces*, *87*(1), pp.159-163.

15. Ghahremanzadeh, R., Yazdi Samadi, F. and Yousefi, M., 2019. Green synthesis of gold nanoparticles using three medicinal plant extracts as efficient reducing agents. *Iranian Journal of Chemistry and Chemical Engineering (IJCCE)*, *38*(1), pp.1-10.

16. Patra, J.K., Das, G., Fraceto, L.F., Campos, E.V.R., del Pilar Rodriguez-Torres, M., Acosta-Torres, L.S., Diaz-Torres, L.A., Grillo, R., Swamy, M.K., Sharma, S. and Habtemariam, S., 2018. Nano based drug delivery systems: recent developments and future prospects. *Journal of nanobiotechnology*, *16*(1), pp.1-33.

17. Preeti, K., Balaram, G. and Swati, B., 2015. Nanocarriers for cancer-targeted drug delivery. *J. Drug Target*.

18. Adeyemi, O.S. and Sulaiman, F.A., 2015. Evaluation of metal nanoparticles for drug delivery systems. *Journal of biomedical research*, *29*(2), p.145.

19. Modugno, G., Ménard-Moyon, C., Prato, M. and Bianco, A., 2015. Carbon nanomaterials combined with metal nanoparticles for theranostic applications. *British journal of pharmacology*, *172*(4), pp.975-991.

20. Salman, S.A., Kuroda, K. and Okido, M., 2013. Preparation and characterization of hydroxyapatite coating on AZ31 Mg alloy for implant applications. Bioinorganic chemistry and applications, 2013.

21. Mohanraj VJ, Chen Y. Nanoparticles-a review. Tropical journal of pharmaceutical research. 2006;5(1):561-73.

22. Liying HE, Yumin SU, Lanhong J, Shikao SH. Recent advances of cerium oxide nanoparticles in synthesis, luminescence and biomedical studies: a review. Journal of

rare earths. 2015 Aug 1;33(8):791-9.

23. Rajeshkumar S, Naik P. Synthesis and biomedical applications of cerium oxide nanoparticles–a review. Biotechnology Reports. 2018 Mar 1;17:1-5.

24. Magudieshwaran R, Ishii J, Raja KC, Terashima C, Venkatachalam R, Fujishima A, Pitchaimuthu S. Green and chemical synthesized CeO2 nanoparticles for photocatalytic indoor air pollutant degradation. Materials Letters. 2019 Mar 15;239:40-4.

25. Nadeem M, Tungmunnithum D, Hano C, Abbasi BH, Hashmi SS, Ahmad W, Zahir A. The current trends in the green syntheses of titanium oxide nanoparticles and their applications. Green chemistry letters and reviews. 2018 Oct 2;11(4):492-502.

26. Srikar SK, Giri DD, Pal DB, Mishra PK, Upadhyay SN. Green synthesis of silver nanoparticles: a review. Green and Sustainable Chemistry. 2016 Feb 16;6(1):34-56.