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REVIEW ARTICLE

Nanoparticles in Inner Ear Diseases

Soumick Ranjan Sahoo[1,*]

[1]*Ent Department, Steel Authority of India Limited, IISCO Steel Plant, Burnpur Hospital, West Bengal, India*

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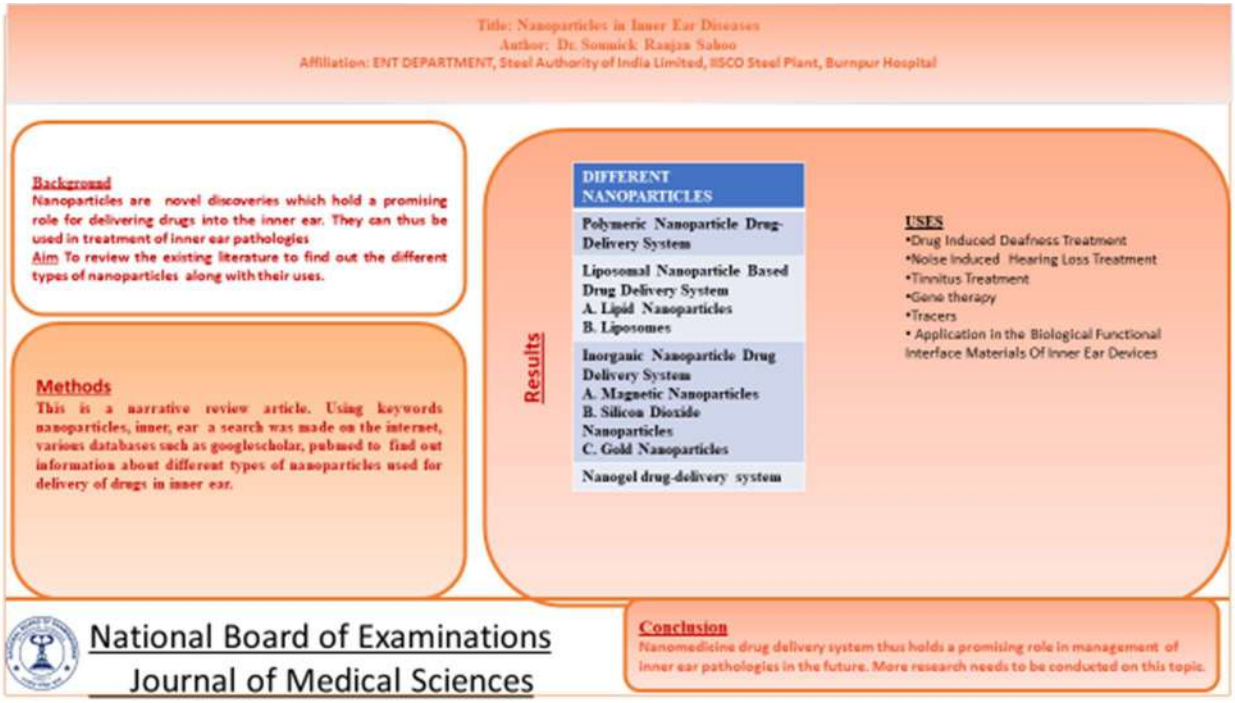
Abstract

Nanoparticles are novel discoveries which hold a promising role for delivering medications into the inner ear in the future. Nanoparticles are formed by the preparation of different biomaterials. They are capable of encapsulating various types of medications. The various nanoparticle drug delivery systems include polymers, liposomal Nanoparticles, magnetic Nanoparticles, silicon dioxide Nanoparticles, gold Nanoparticles and nanogels which will be briefly discussed in this narrative review article.

Keywords: Nanoparticles, Inner, Ear

*Corresponding Author: Soumick Ranjan Sahoo
Email: soumicksahoo@gmail.com

Graphical Abstract



Introduction

Nanomedicine can be defined as a complex, multi-disciplinary branch of medicine, in which nano-bio-technologies, and other nano-sciences are applied at every step of disease management which includes diagnosis, treatment, prognosis, and monitoring of biological parameters and biomarkers [1,2]. The term “nanomedicine” was coined by the American engineer Eric Drexler (1955) and Robert Freitas Jr. (1952) in the nineties [3], with the publication of the multi-volume textbook entitled “Nanomedicine”, released in October 1999.

Moreover different super-specialties such as nano-surgery [4,5], nano-neurosurgery [6,7] nano-otorhinolaryngology [8], nano-dentistry [9], nano-ophthalmology [10], nano-neurology [11], nano-cardiology [12], nano-orthopedics [11], nano-infectiology [11], and nano-oncology [13], among others [11], are emerging within nanomedicine.

The countries with the highest percentages of articles in the field of nanomedicine were North America (38.3%) and Europe (35.1%) [1].

In recent years, regions such as China, India, and South Korea have been productive in this field of nanomedicine [1]. In India ICMR is responsible for the promotion of biomedical research and has funded 154 projects on studies related to nanomedicine [14].

Nanomedicine In Inner Ear Diseases

Hearing loss is an important health issue faced by mankind. Amongst the many pathologies causing hearing loss,inner ear pathologies have a significant contribution. The various types of inner ear disorders where the therapeutic interventions are

required include Menieres disease,ssnhl,acoustic shock etc. These therapeutic drugs such as steroids are delivered by systemic route and intratympanic injection (Figure 1).

Due to complexity of blood labyrinth barrier therapeutic drugs given by systemic route find it difficult to reach their site of action. In case of direct inner ear delivery drugs are delivered directly into the inner ear [15].

Nanoparticles are novel discoveries which hold a promising role for delivering medications into the inner ear in the future. Various types of biomaterials are used for forming nanoparticles. These biomaterials have the ability of encapsulating various types of drugs used for therapeutic purposes [15] Higher biocompatibility, better drug stability, high controlled drug release and targeting by surface modification are some of the advantages of nanoparticles.

The various types of nanoparticle drug delivery systems are as follows:

1. Polymeric Nanoparticle Drug-Delivery System

This system includes poly(lactic-co-glycolic acid) (PLGA) which is a biodegradable polymer. Numerous advantages include good biocompatibility and hydrophilicity along with controlled degradation [15]. The target area of delivery of drugs is scala tympani through the *trans*-Round Window Membrane injection.

The route of diffusion of these nanoparticles after the intratympanic injections have been reported by researchers [16].

Using guinea pig cochlea a novel drug-delivery system has been developed by researchers. [17]

Other examples of polymeric nanoparticles include polylactic acid, polycaprolactone and PEG. They have been used for the treatment of inner ear diseases [18-20]

2. Liposomal Nanoparticle Based Drug Delivery System

A. Lipid Nanoparticle

They are biodegradable and both hydrophilic and lipophilic drugs can be delivered thorugh this type of nanoparticle. [15,21,22]. Various diseases have been treated by using solid lipid nanoparticles (SLNs) as novel drug-delivery systems [23-25].

There are numerous benefits like low cost, easy scale-up of SLNs production and proven production method [26].

Researchers have reported SLNs based on stearic acid as excellent nanocarriers for drug delivery.[26]

B. Liposomes

They have numerous benefits like improved stability, nontoxicity, high biocompatibility etc [15,27]. Recent advances in targeting ligand design have led to clinically promising and efficient drug-delivery systems with targeting ligands.Examples include peptides [28,29], antibodies [30,31], oligonucleotide aptamers [32,33] and folic acid [34].

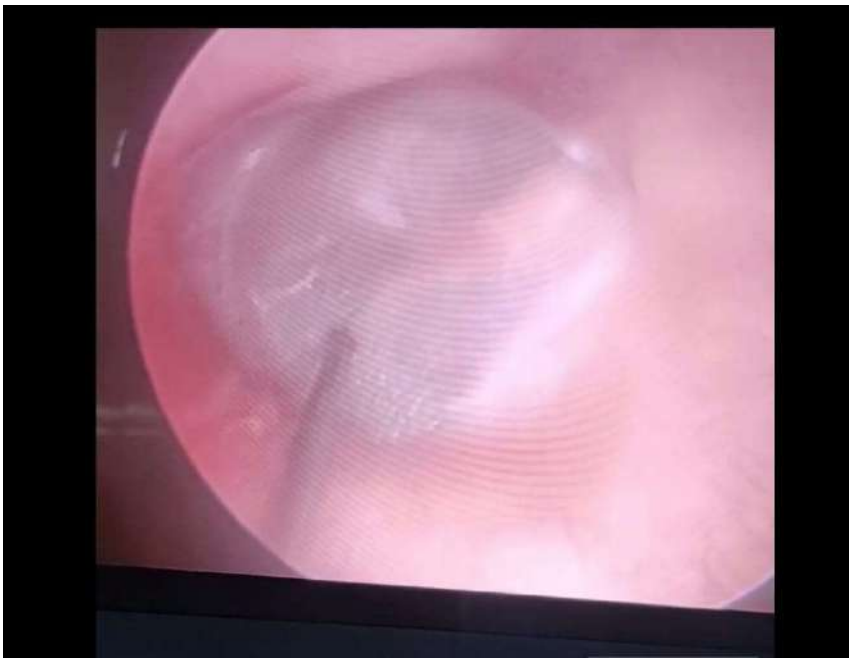


Figure 1: Intratympanic injection of steroid.

It has been shown that drugs can be carried across the Round Window Membrane by liposomes leading to delivery of drugs into the inner ear cells. [35,36]

3. Inorganic Nanoparticle Drug Delivery System

A. Magnetic Nanoparticles

Various benefits of this type of nanoparticle drug delivery system includes less toxicity, greater biocompatibility and convenient manipulation [15]. The representative of this category is superparamagnetic iron oxide Nanoparticles (SPION). Specific advantages include:

Magnetic responsiveness [37]
Superparamagnetism [38]
Small particle size [39]

An *in vitro* Round Window Membrane model was designed through which SPION could be transported thus allowing the quantitative assessment of the expected targeted drug or gene delivery [40].

Irreversible and bilateral sensorineural deafness is a side effect of cisplatin used for treating head and neck tumors [41,42]. To solve this side effect,. a novel nanostructure was designed by Kayyali *et al* composed of SPION [43].

B. Silicon dioxide Nanoparticles

Numerous advantages include greater drug-loading capacity, greater yield and less production cost [15]. The commonest choice is silica and is being used in biomedical applications. Amongst them Mesoporous silica Nanoparticles preferred over other porous silica Nanoparticles. Mesoporous silica supraparticulate delivery systems have been used for evaluation of the pharmacokinetics and biodistribution of exogenous neurotrophin-3 delivered by this system in the inner ear [44].

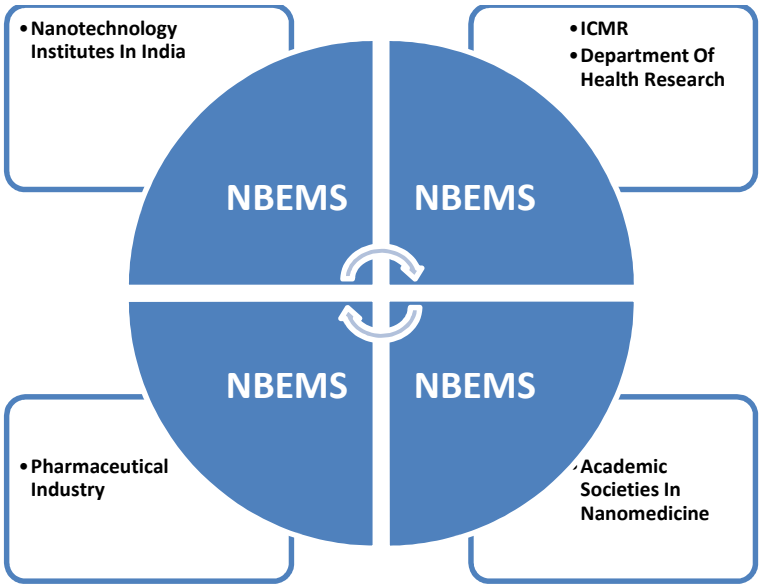


Figure 2: NBEMS Model of Nanomedicine Research.

C. Gold Nanoparticles

These nanoparticles have been used in the treatment of tumors and in bioimaging [15]. The advantages include their distinctive optical properties and higher biocompatibility [45].

They have been used as an effective drug and gene delivery vehicle for treating inner ear pathology [46].

4. Nanogel drug-delivery system

This nanoparticle has distinctive hydrogel properties and nanoporous structure [15,47]. This makes this nanoparticle a potential drug-delivery carrier [15,47]. Numerous advantages of this system includes high biocompatibility, long circulation time, small size of the particle.

A minimally invasive nanohydrogel drug-delivery system was developed by researchers in 2015 [19].

Modifications were performed by researchers for introducing a targeting peptide to specifically recognize prestin [48].

To address issue of cisplatin ototoxicity a dextran–PEG hydrogel delivery system was designed and investigated using mouse model [49].

Applications [50]

- Drug Induced Deafness Treatment
- Noise Induced Hearing Loss Treatment
- Tinnitus Treatment
- Gene therapy
- Tracers
- Application in the Biological Functional Interface Materials of Inner Ear Devices

Limitations

- The interaction between nanomedicine and various molecules, cells and organs of the body is based on a series of complex interactions between particles and biological media. [50]
- Sometimes nanoparticles can be toxic and damage the immune system. [50]

Conclusion

Nanomedicine drug delivery system thus holds a promising role in management of inner ear pathologies in the future. More research needs to be conducted on this topic. A coordinated approach of various centres doing research in nanotechnology is required. A model is being proposed (Figure 2) which will help in manufacturing nanoparticles in India and their clinical application in patients.

Ethics declarations

Funding This study did not receive any funding.

Conflict of interest

The authors declare that they have no competing interests.

Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability

Not applicable.

References

1. Bragazzi NL. Nanomedicine: Insights from a Bibliometrics-Based Analysis of Emerging Publishing and Research Trends. Medicina (Kaunas). 2019 Dec 15;55(12):785. doi: 10.3390/medicina55120785.
2. Freitas R.A., Jr. What is nanomedicine? *Nanomedicine.* 2005;1:2–9. doi: 10.1016/j.nano.2004.11.003.
3. Sun M., Sen Gupta A. Vascular Nanomedicine: Current Status, Opportunities, and Challenges. *Semin. Thromb. Hemost.* 2019 doi: 10.1055/s-0039-1692395.
4. Gayathri Vegesna N.V., Ronchi P., Durdu S., Terjung S., Pepperkok R. Targeted Ablation Using Laser Nanosurgery. *Methods Mol. Biol.* 2017;1563:107–125.
5. Zeigler M.B., Chiu D.T. Single-cell nanosurgery. *Methods Mol. Biol.* 2013;991:139–148.
6. Andrews R.J. Neuroprotection at the nanolevel—Part I: Introduction to nanoneurosurgery. *Ann. N. Y. Acad. Sci.* 2007;1122:169–184. doi: 10.1196/annals.1403.012.
7. Leary S.P., Liu C.Y., Apuzzo M.L. Toward the emergence of nanoneurosurgery: Part II—Nanomedicine: Diagnostics and imaging at the nanoscale level. *Neurosurgery.* 2006;58:805–823. doi: 10.1227/01.NEU.0000216793.45952.ED.
8. Bragazzi N.L. Nano-otorhinolaryngology: State of the art and future perspectives. *Otolaryngol.* 2015;5:2. doi: 10.4172/2161-119X.S1.007.
9. Aeran H., Kumar V., Uniyal S., Tanwer P. Nanodentistry: Is just a fiction or future. *J. Oral Biol. Craniofac. Res.* 2015;5:207–211. doi: 10.1016/j.jobcr.2015.06.012.
10. Kamaleddin M.A. Nano-ophthalmology: Applications and considerations. *Nanomedicine.* 2017;13:1459–1472. doi: 10.1016/j.nano.2017.02.007
11. Jain K.K. Nanomedicine: Application of nanobiotechnology in medical practice. *Med. Princ. Pract.* 2008;17:89–101. doi: 10.1159/000112961.
12. Spivak M.Y., Bubnov R.V., Yemets I.M., Lazarenko L.M., Tymoshok N.O., Ulberg Z.R. Gold nanoparticles—The theranostic challenge for PPPM: Nanocardiology application. *EPMA J.* 2013;4:18. doi: 10.1186/1878-5085-4-18.
13. Goel S., Chen F., Cai W. Highlights from the latest articles in nano-

oncology. *Nanomedicine.* 2015;10:897–898. doi: 10.2217/nnm.14.220.

14. Bhatia, Pooja, Vasaikar, Suhas and Wali, Anil. "A landscape of nanomedicine innovations in India" *Nanotechnology Reviews*, vol. 7, no. 2, 2018, pp. 131-148. https://doi.org/10.1515/ntrev-2017-0196
15. Zhang L, Bai X, Wang R, Xu L, Ma J, Xu Y, Lu Z. Advancements in the studies of novel nanomaterials for inner ear drug delivery. Nanomedicine (Lond). 2022 Aug;17(20):1463-1475. doi: 10.2217/nnm-2022-0121.
16. Zhang L, Xu Y, Cao W, Xie S, Wen L, Chen G. Understanding the translocation mechanism of PLGA nanoparticles across round window membrane into the inner ear: a guideline for inner ear drug delivery based on nanomedicine. *Int. J. Nanomed.* 13, 479–492 (2018).
17. Dai J, Long W, Liang Z, Wen L, Yang F, Chen G. A novel vehicle for local protein delivery to the inner ear: injectable and biodegradable thermosensitive hydrogel loaded with PLGA nanoparticles. *Drug Dev. Ind. Pharm.* 44(1), 89–98 (2018).
18. El Kechai N, Agnely F, Mamelle E, Nguyen Y, Ferrary E, Bochot A. Recent advances in local drug delivery to the inner ear. *Int. J. Pharm.* 494(1), 83–101 (2015).
19. Lajud SA, Nagda DA, Qiao P et al. A novel chitosan-hydrogel-based nanoparticle delivery system for local inner ear application. *Otol. Neurotol.* 36(2), 341–7 (2015).
20. Vigani B, Rossi S, Sandri G, Bonferoni MC, Caramella CM, Ferrari F. Hyaluronic acid and chitosan-based nanosystems: a new dressing generation for wound care. *Expert Opin Drug Deliv.* 16(7), 715–740 (2019).
21. Dawoud MZ, Nasr M. Comparison of drug release from liquid crystalline monoolein dispersions and solid lipid nanoparticles using a flow cytometric technique. *Acta Pharm. Sin. B* 6(2), 163–169 (2016).
22. Teixeira MC, Carbone C, Souto EB. Beyond liposomes: recent advances on lipid based nanostructures for poorly soluble/poorly permeable drug delivery. *Prog. Lipid Res.* 68, 1–11 (2017).
23. Arana L, Salado C, Vega S et al. Solid lipid nanoparticles for delivery of *Calendula officinalis* extract. *Colloids Surf. B Biointerfaces* 135, 18–26 (2015).
24. Arana L, Bayón-Cordero L, Sarasola LI, Berasategi M, Ruiz S, Alkorta I. Solid lipid nanoparticles surface modification modulates cell internalization and improves chemotoxic treatment in an oral carcinoma cell line. *Nanomaterials (Basel)* 9(3), 464 (2019).
25. Raza A, Sime FB, Cabot PJ, Maqbool F, Roberts JA, Falconer JR. Solid nanoparticles for oral antimicrobial drug delivery: a review. *Drug Discov. Today* 24(3), 858–866 (2019).
26. Cervantes B, Arana L, Murillo-Cuesta S et al. Solid lipid nanoparticles loaded with glucocorticoids protect auditory cells from cisplatin-induced ototoxicity. *J. Clin. Med.* 8(9), 1464 (2019).
27. Panahi Y, Farshbaf M, Mohammadhosseini M et al. Recent advances on liposomal nanoparticles: synthesis, characterization and biomedical applications. *Artif. Cells Nanomed. Biotechnol.* 45(4), 788–799 (2017).
28. Shin MC, Zhang J, Min KA et al. Cell-penetrating peptides: achievements and challenges in application for cancer treatment. *J. Biomed. Mater. Res. A* 102(2), 575–587 (2014).
29. Qin L, Wang CZ, Fan HJ et al. A dual-targeting liposome conjugated with transferrin and arginine-glycine- aspartic acid peptide for glioma-targeting

therapy. *Oncol. Lett.* 8(5), 2000–2006 (2014).
30. Saeed M, van Brakel M, Zalba S et al. Targeting melanoma with immunoliposomes coupled to anti-MAGE A1 TCR-like single-chain antibody. *Int. J. Nanomed.* 11, 955–975 (2016).
31. Yue PJ, He L, Qiu SW et al. OX26/CTX-conjugated PEGylated liposome as a dual-targeting gene delivery system for brain glioma. *Mol. Cancer* 13, 191 (2014).
32. Esposito CL, Catuogno S, de Franciscis V. Aptamer-mediated selective delivery of short RNA therapeutics in cancer cells. *J. RNAi Gene Silencing* 10, 500–506 (2014).
33. Wu YY, Hsieh IS, Tung CH et al. A novel DNA aptamer targeting lung cancer stem cells exerts a therapeutic effect by binding and neutralizing annexin A2. *Mol. Ther. Nucleic Acids* 27, 956–968 (2022).
34. Cui SH, Zhi DF, Zhao YN et al. Cationic lioposomes with folic acid as targeting ligand for gene delivery. *Bioorg. Med. Chem. Lett.* 26(16), 4025–4029 (2016).
35. Meyer H, Stöver T, Fouchet F et al. Lipidic nanocapsule drug delivery: neuronal protection for cochlear implant optimization. *Int. J. Nanomed.* 7, 2449–2464 (2012).
36. Hou S, Yang Y, Zhou S et al. Novel SS-31 modified liposomes for improved protective efficacy of minocycline against drug-induced hearing loss. *Biomater. Sci.* 6(6), 1627–1635 (2018).
37. Obireddy SR, Lai WF. ROS-generating amine-functionalized magnetic nanoparticles coupled with carboxymethyl chitosan for pH-responsive release of doxorubicin. *Int. J. Nanomed.* 17, 589–601 (2022).
38. Martín MJ, Spitzmaul G, Lassalle V. Novel insights and perspectives for the diagnosis and treatment of hearing loss through the implementation of magnetic nanotheranostics. *ChemMedChem* 17(5), e202100685 (2022).
39. Hu Y, Li D, Wei H et al. Neurite extension and orientation of spiral ganglion neurons can be directed by superparamagnetic iron oxide nanoparticles in a magnetic field. *Int. J. Nanomed.* 16, 4515–4526 (2021).
40. Mondalek FG, Zhang YY, Kropp B et al. The permeability of SPION over an artificial three-layer membrane is enhanced by external magnetic field. *J. Nanobiotechnol.* 4, 4 (2006).
41. Knight KR, Chen L, Freyer D et al. Group-wide, prospective study of ototoxicity assessment in children receiving cisplatin chemotherapy (ACCL05C1): a report from the children's oncology group. *J. Clin. Oncol.* 35(4), 440–445 (2017).
42. Sheth S, Mukherjea D, Rybak LP, Ramkumar V. Mechanisms of cisplatin-induced ototoxicity and otoprotection. *Front. Cell. Neurosci.* 11, 338 (2017).
43. Kayyali MN, Ramsey AJ, Higbee-Dempsey EM et al. The development of a nano-based approach to alleviate cisplatin-induced ototoxicity. *J. Assoc. Res. Otolaryngol.* 19(2), 123–132 (2018).
44. Gunewardene N, Lam P, Ma Y et al. Pharmacokinetics and biodistribution of supraparticle-delivered neurotrophin 3 in the guinea pig cochlea. *J. Control Release* 342, 295–307 (2022).
45. Yang Z, Wang D, Zhang C et al. The applications of gold nanoparticles in the diagnosis and treatment of gastrointestinal cancer. *Front. Oncol.* 11, 819329 (2022).
46. Lin YC, Shih CP, Chen HC et al. Ultrasound microbubble-facilitated inner ear delivery of gold nanoparticles involves transient disruption of the tight junction barrier in the round window membrane. *Front. Pharmacol.* 12, 689032 (2021).

47. Merino S, Martín C, Kostarelos K, Prato M, Vázquez E. Nanocomposite hydrogels: 3D polymer-nanoparticle synergies for on-demand drug delivery. *ACS Nano* 9(5), 4686–4697 (2015).
48. Kayyali MN, Wooltorton JRA, Ramsey AJ et al. A novel nanoparticle delivery system for targeted therapy of noise-induced hearing loss. *J. Control Release* 279, 243–250 (2018).
49. Chen Y, Gu J, Liu J et al. Dexamethasone-loaded injectable silk-polyethylene glycol hydrogel alleviates cisplatin-induced ototoxicity. *Int. J. Nanomed.* 14, 4211–4227 (2019).
50. Li L, Luo J, Lin X, Tan J, Li P. Nanomaterials for Inner Ear Diseases: Challenges, Limitations and Opportunities. Materials (Basel). 2022 May 25;15(11):3780. doi: 10.3390/ma15113780.