RESEARCH ARTICLE

Silver and Iron Nanoparticles: Green Synthesis and Characterization

Ravindra Waykar*, Srinivasakumar Kumarapillai

Faculty of Pharmacy, Lincoln University College, Petaling Jaya, Selangor Darul Ehsan, Malaysia.

Received: 20th February, 2024; Revised: 27th March, 2024; Accepted: 05th August, 2024; Available Online: 25th September, 2024

ABSTRACT

Biosynthesized nanoparticles (NPs) are gaining traction because they leverage physiologically active plant secondary metabolites, enabling eco-friendly synthesis and offering exclusive biological benefits. This innovative nanomedicine technology shows great promise in medicine, providing a novel method for drug delivery and treatment. The advancement of biosynthesized nanomedicine has notable implications for the pharmaceutical and medical sectors, presenting a more precise and effective way to address diseases. This paper introduces a cost-effective, environmentally friendly, and dependable method for synthesizing silver and iron NPs. The method involves employing the aqueous leaf extract of *Vallisneria spiralis* Linnaeus. The biosynthesized NPs were analyzed utilizing several methods, including transmission electron microscope (TEM), dynamic light scattering (DLS), UV−visible spectroscopy, and ICP-MS.

Keywords: *Vallisneria spiralis*, Ag-NPs, Fe-NPs, Green synthesis, Characterization.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.3.20

How to cite this article: Waykar R, Kumarapillai S. Silver and Iron Nanoparticles: Green Synthesis and Characterization. International Journal of Drug Delivery Technology. 2024;14(3):1389-1395.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Biosynthesized nanomedicine refers to the usage of biological processes in the direction of producing nanoparticles (NPs) that are employed in medical applications, for example drug delivery and imaging. While the provided context does not explicitly define biosynthesized nanomedicine, it can be inferred that this approach involves leveraging the exclusive properties of NPs synthesized through biological means for therapeutic and diagnostic purposes.[1-3] The history and development of nanotechnology in medicine, often termed nanomedicine, have been marked by significant milestones. Nanotechnology's inception dates back to the conceptualization of manipulating matter at the nanoscale, with subsequent advancements leading to its application in several medical fields, including drug delivery, imaging, and regenerative medicine. The evolution of nanomedicine has been characterized by interdisciplinary efforts to harness nanoscale materials for improving medical interventions.[4-6] Nanotechnology's importance and significance in medicine are profound. It has revolutionized healthcare by enabling targeted drug delivery (TDDS) systems that improve therapeutic outcomes and reduce side effects, enhancing the precision of medical diagnostics and fostering innovations in regenerative medicine. NPs' ability in the direction of penetrating biological barriers as well as gathering next to disease locations has increased the bioavailability of therapeutic agents, while novel contrast agents based on nanomaterials have improved imaging techniques. Additionally, nanomaterials have been instrumental in advancing tissue engineering and organ transplantation.[7-10] The biosynthesized nanomedicine is an emerging field that utilizes biologically produced NPs for medical applications. Nanotechnology has enabled more effective and precise medical interventions, highlighting its critical role in advancing medicine.[11-13]

Biosynthesized nanomedicines show significant promise for TDDS, medical diagnostics and imaging, cancer therapy, wound healing, and tissue engineering. TDDS is enhanced by the use of NPs, which can be functionalized in the direction of delivering therapeutic agents unswervingly to specific sites, thereby increasing efficacy and dropping side effects.[14-17] In the realm of diagnosis and imaging, NPs offer novel approaches for molecular imaging and early diagnosis, particularly in cancer treatment, where early detection is crucial for successful outcomes.[18-20] Interestingly, while cancer therapy and wound healing are distinct fields, they both benefit from the advancements in nanomedicine. NPs are being developed to improve chemotherapy delivery for cancer and enhance wound healing and tissue regeneration by boosting cell growth and differentiation.[21-26] The biosynthesized nanomedicine is a multifaceted field with applications that span from TDDS systems that improve therapeutic outcomes to innovative approaches in cancer therapy.[27-30] Additionally, the role of nanomedicine in wound healing and tissue engineering is underscored by its contribution to improved healing

*Author for Correspondence: writetome@zeonhealth.net

processes and tissue regeneration.[31-34] The integration of these applications demonstrates the broad potential of nanomedicine to revolutionize treatment strategies across several medical disciplines.

Biosynthesized nanomedicines offer several advantages, including biocompatibility and low toxicity. Biocompatibility is crucial for any therapeutic agent, as it ensures that the nanomedicine can interact with biological systems without eliciting an adverse immune response. Bottini and Bottini (2012) highlighted that carbon nanotubes have enhanced solubility, improved biocompatibility, and no toxic effects after injection in living animals.[35] Similarly, Madgula *et al*. (2023) emphasize that biologically synthesized nanocarriers are designed to be biodegradable and possess excellent biocompatibility, which is essential for reducing cytotoxicity and preventing the accumulation of the drug in non-target areas.[36] In addition to biocompatibility, biosynthesized nanomedicines are known for their enhanced stability and controlled release properties. Willis *et al*. (2012) discuss therapeutic liposomal powders for pulmonary delivery, which exhibit controlled drug release and increased formulation stability.[37] Pandolfi *et al*. (2016) described the controlled release of bioactive compounds that are advantageous for tissue regeneration.[38] Biosynthesized nanomedicines are advantageous due to their biocompatibility, reduced risk of side effects, and ability to provide stable, controlled release, improving treatment effectiveness and safety.

Nanomedicine, particularly when biosynthesized, offers significant advantages in the realm of targeted therapy and personalized medicine. NPs high surface-to-volume ratio and adjustable surface chemistry allow targeted delivery of drugs to specific tissues, improving efficacy and reducing side effects. Their multifunctional nature also supports simultaneous delivery of multiple drugs tailored to individual patient needs.[39-41] Interestingly, while the focus is often on cancer treatment, the benefits of biosynthesized nanomedicine extend to other diseases as well. For instance, in bone diseases like osteoporosis, NPs can enhance drug delivery and therapeutic effectiveness, offering site-specific targeting and controlled drug release.[42-44] Additionally, in the context of incapacitating drug resistance in malignancy, targeted nanomedicine strategies can enhance drug uptake and intracellular accumulation, addressing the challenge of multidrug resistance (MDR).[45-48] Biosynthesized nanomedicine enables targeted drug delivery by designing nanoparticles that navigate the complex *in-vivo* environment to reach specific sites effectively. The multifunctional capabilities of these nanocarriers also support combination therapies and the advancement of personalized medicine by allowing for the customization of treatment regimens based on individual patient profiles. These advantages underscore the transformative potential of nanomedicine in enhancing therapeutic outcomes across a spectrum of diseases.

Research in biosynthesized nanomedicine focuses on developing advanced nanotherapeutics to enhance clinical outcomes.[49-52] Nanotechnology in medicine shows promise in preclinical cancer studies and may address the restrictions of conventional treatments.[53-56] Nevertheless, the translation of these nanomedicines from bench to bedside is fraught with challenges. These include poor reproducibility in high-volume production, complexities in tumor biology, and an incomplete understanding of nano-bio interactions, which have led to failures in animal studies and clinical trials.[57-59] Advancements in microfluidics and engineering enhance the potential for clinical translation and commercialization of biosynthesized nanomedicine. Despite the hurdles, there is significant encouragement for nanomedicines because of their ability to address diverse disease challenges and the progress made in the field so far. Overcoming barriers like safety, pharmacokinetics, manufacturing, affordability, and regulation is essential to fully realize the potential of these innovations.[60-63] The future of biosynthesized nanomedicine is promising, with ongoing research tackling current limitations and challenges. The potential for clinical translation and commercialization is evident, but it requires a concerted effort to navigate the complex landscape of safety, efficacy, manufacturing, and regulatory considerations. Advancements in nanotechnology are poised for significant advancements, provided that the barriers to innovation and access are effectively addressed.[64-66]

MATERIALS AND METHODS

Materials

All chemicals and reagents utilized during experimentation were of analytical grade and were obtained from Hi-Media.

Methods

Extract preparation

Vallisneria spiralis Linnaeus (*Vallisneria spiralis* L.) leaves were collected from Kanyakumari, India. *Vallisneria spiralis* L. leaves were rinsed, air-dried, and ground into powder. About 25 g of the powder were mixed with 250 mL of water, heated to 80°C, and stirred for 3 hours. The mixture was then filtered and stored at 4°C.

Green synthesis of Ag-NPs

Ag-NPs were synthesized using the leaf extract of *Vallisneria spiralis* L. 10 mL of this extract was mixed with 90 mL of 1 mM silver nitrate solution, heated to 80°C, and stirred for 3 hours. The solution, which changed color from yellow to dark gray, was then cooled for 12 hours and matured for another 24 hours. The Ag-NPs were separated by centrifugation at 15,000 rpm for 20 minutes, freeze-dried, and stored at 4°C.

Green synthesis of Fe-NPs

Fe-NPs were synthesized using FeCl3 and sphagnum extract. 10ml of the extract was added to 100 mL of 0.012M $FeCl_3$ solution, heated to 90°C, and stirred for 2 hours. The mixture changed from yellow to dark red, indicating Fe-NP formation. After cooling for 12 hours and maturing for 24 hours, the particles were centrifuged at 13,000 RPM for 60 minutes at +4°C and rinsed three times with distilled water.

Nanoparticle Characterization

NPs size and stability

The size as well as shape of NPs are important elements that can influence several aspects, including colloidal stability.[69] Dynamic light scattering (DLS) is a crucial method utilized in the direction of analyzing and describing NPs and other colloidal solutions.[70] DLS quantifies the light that is diffused by a laser as it traverses a colloidal solution. By examining the changes in the intensity of scattered light over time, one may gather information about the size of the particle in a solution. The research relies on the diffusive mobility of particles in a solution, known as Brownian motion. The hydrodynamic diameter refers to the diameter of an imaginary sphere that diffuses at the same pace as the particles being studied and is determined by analyzing the time-dependent scattering intensity measurements.[71] The repulsive force between suspended NPs arises from the variation in ZP, which is influenced by the augmentation of surface charge on the particles. Zeta Potential (ZP) measures the electrical potential difference between a nanoparticle's surface and its surrounding fluid, indicating dispersion stability. The hydrodynamic diameters and ZPs of nanoparticles were assessed using the Zetasizer Nano ZS, evaluating size and charge under varying pH conditions.

Transmission electron microscopy (TEM)

TEM is a precise technique for measuring high-magnification pictures of electron beams passing through NPs.[73] The imaging contrast in the transmitted beam is determined by the amplitude and phase variations, which are influenced by the sample thickness and material composition. The essential features of NPs are their mass, volume, and concentration. The volume of a nanoparticle is calculated by measuring its dimensions. The main instrument employed for measuring particle size and subsequently calculating their volume was a TEM. We utilized a JEOL 1010 transmission electron microscope.

Elemental concentration

After calculating the volume of the nanoparticle, the mass can be easily computed by multiplying the volume by the density of the substance.[74] We engaged Inductively Coupled Plasma Mass Spectrometry (ICP-MS), make Agilent to directly quantify the elemental concentration of nanoparticle solution.

UV-Visible spectroscopic analysis

UV-visible spectroscopy, using an Agilent 8453 spectrometer, measures light absorption and scattering by nanoparticles in the 200 to 1100 nm range with a 1 nm slit width.[75-78]

RESULTS AND DISCUSSION

Measurements conducted in the UV-visible spectroscopy revealed that VS-Ag-NPs optical properties exhibited in Figure 1 and VS-Fe-NPs optical properties exhibited in Figure 2.

The TEM technique was utilized in the direction of analyzing the morphology of the VS-Ag-NPs and VS-Fe-NPs that were produced utilizing a green synthesis. The produced

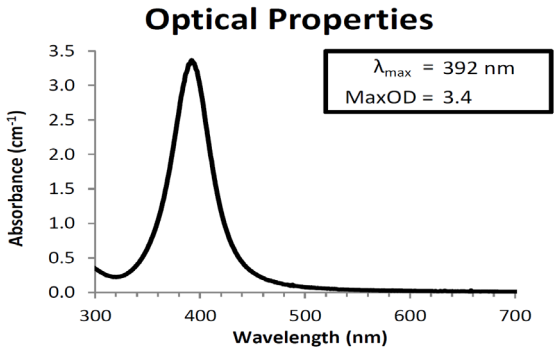


Figure 1: Absorption spectra of VS-Ag-NPs

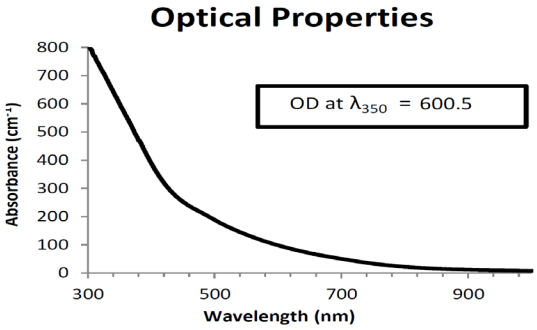


Figure 2: Absorption spectra of VS-Fe-NPs

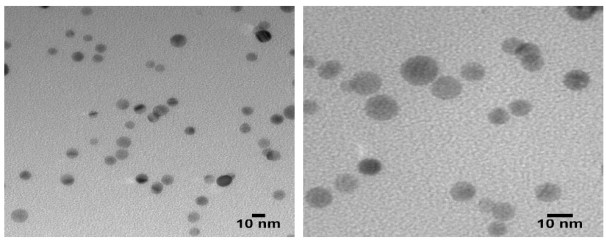


Figure 3: TEM microscopy of VS-Ag-NPs

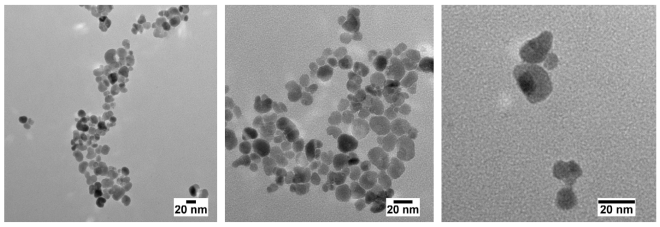


Figure 4: TEM microscopy of VS-Fe-NPs

VS-Ag-NPs showed a spherical morphology, as seen in Figure 3. The produced VS-Fe-NPs exhibited a spherical morphology, with some particles displaying uneven granulation and aggregation, as seen in Figure 4.

The TEM investigation revealed that the average size of VS-Ag-NPs was 10 nm, as seen in Figure 5 and the average size of VS-Fe-NPs ranged was 20 nm, as seen in Figure 6.

At pH 8.2, the hydrodynamic diameter (Dh) was 20 nm, ZP (ζ) was -33 mV, the mass concentration of silver was

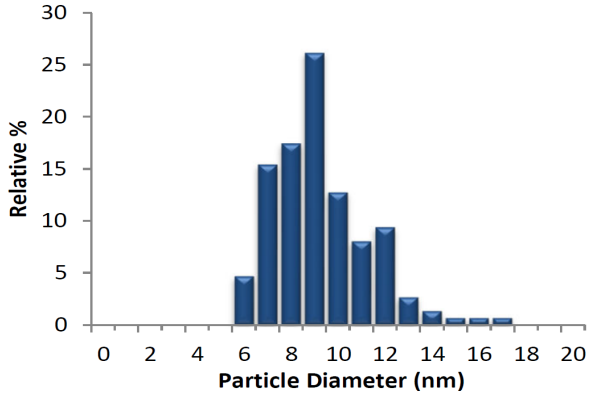


Figure 5: Size distribution plot of VS-Ag-NPs

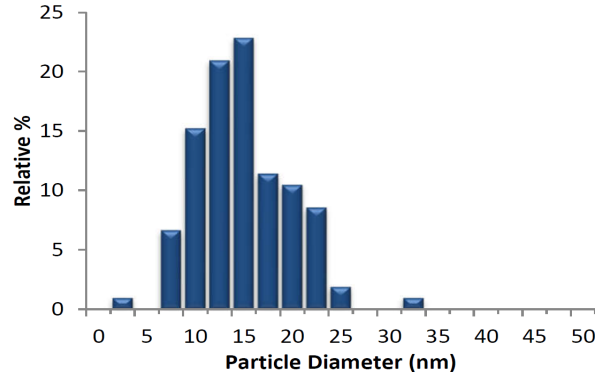


Figure 6: Size distribution plot of VS-Fe-NPs

0.021 mg/mL, and the particle concentration was 4.1E+12 particles/mL for VS-Ag-NPs. At pH 7.2, Dh was 50 nm, ζ was -48 mV, the mass concentration of iron was 20.13 mg/mL, and the particle concentration was 1.7E+15 particles/mL for VS-Fe-NPs.

CONCLUSION

Green synthesized nanomedicines are generally embraced in the medical field because of their several benefits for human health and their minimal likelihood of causing negative effects. The Ag-NPs and Fe-NPs were synthesized from the plant leaf extract of *Vallisneria spiralis* L. utilizing a straightforward and convenient green method that does not require any specific instruments. The Ag-NPs and Fe-NPs synthesized with a green method can be effectively utilized as treatments and carriers for drug delivery.

ACKNOWLEDGMENT

None.

REFERENCES

1. Adeyemi JO, Oriola AO, Onwudiwe DC, Oyedeji AO. Plant Extracts Mediated Metal-Based NPs: Synthesis and Biological Applications. Biomolecules. 2022;12(5):627. DOI: https://doi.org/10.3390/biom12050627
2. Mustapha T, Misni N, Ithnin NR, Daskum AM, Unyah NZ. A Review on Plants and Microorganisms Mediated Synthesis of Silver NPs, Role of Plants Metabolites and Applications. International Journal of Environmental Research and Public Health. 2022;19(2):674. DOI: https://doi.org/10.3390/ijerph19020674
3. Haider FU, Zulfiqar U, Ul Ain N, *et al*. Harnessing plant extracts for eco-friendly synthesis of iron nanoparticle (Fe-NPs): Characterization and their potential applications for ameliorating environmental pollutants. Ecotoxicology and Environmental Safety. 2024;281:116620. DOI: https://doi.org/10.1016/j.ecoenv.2024.116620
4. Mbunge E, Muchemwa B, Batani J. Sensors and healthcare 5.0: transformative shift in virtual care through emerging digital health technologies. Global Health Journal. 2021;5(4):169-177. DOI: https://doi.org/10.1016/j.glohj.2021.11.008
5. Ventola CL. The nanomedicine revolution: part 1: emerging concepts. Pharmacy and Therapeutics. 2012;37(9):512-525. DOI: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3462600/
6. Gandhi S, Shastri DH, Shah J, Nair AB, Jacob S. Nasal Delivery to the Brain: Harnessing NPs for Effective Drug Transport. Pharmaceutics. 2024;16(4):481. DOI:10.3390/pharmaceutics16040481
7. Sharma R, Kumar S, Bhawna, *et al*. An Insight of Nanomaterials in Tissue Engineering from Fabrication to Applications. Tissue Engineering and Regenerative Medicine. 2022;19(5):927-960. DOI: https://doi.org/10.1007/s13770-022-00459-z
8. Shokrani H, Shokrani A, Jouyandeh M, *et al*. Green Polymer Nanocomposites for Skin Tissue Engineering. ACS Applied Bio Materials. 2022;5(5):2107-2121. DOI: https://pubs.acs.org/doi/abs/10.1021/acsabm.2c00313
9. Sun R, Wang N, Zheng S, Wang H, Xie H. Nanotechnology-based Strategies for Molecular Imaging, Diagnosis, and Therapy of Organ Transplantation. Transplantation. 2024;108(8):1730-1748. DOI: 10.1097/TP.0000000000004913
10. Tasciotti E, Cabrera FJ, Evangelopoulos M, *et al*. The Emerging Role of Nanotechnology in Cell and Organ Transplantation. Transplantation. 2016;100(8):1629-1638. DOI: 10.1097/TP.0000000000001100
11. Elzein B. Nano Revolution: "Tiny tech, big impact: How nanotechnology is driving SDGs progress. Heliyon. 2024;10(10):e31393. DOI: https://doi.org/10.1016/j.heliyon.2024.e31393
12. Chintapula U, Chikate T, Sahoo D, *et al*. Immunomodulation in age-related disorders and nanotechnology interventions. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2023;15(1):e1840. DOI: https://doi.org/10.1002/wnan.1840
13. Gu S, Luo Q, Wen C, *et al*. Application of Advanced Technologies-Nanotechnology, Genomics Technology, and 3D Printing Technology-In Precision Anesthesia: A Comprehensive Narrative Review. Pharmaceutics. 2023;15(9):2289. DOI: https://doi.org/10.3390/pharmaceutics15092289
14. Akhter MS, Rahman MA, Ripon RK, *et al*. A systematic review on green synthesis of silver NPs using plants extract and their bio-medical applications. Heliyon. 2024;10(11):e29766. DOI: https://doi.org/10.1016/j.heliyon.2024.e29766
15. Andleeb A, Andleeb A, Asghar S, *et al*. A Systematic Review of Biosynthesized Metallic NPs as a Promising Anti-Cancer-Strategy. Cancers (Basel). 2021;13(11):2818. DOI: https://doi.org/10.3390/cancers13112818
16. El-Naggar NE, Shiha AM, Mahrous H, Mohammed ABA. Green synthesis of chitosan NPs, optimization, characterization and antibacterial efficacy against multi drug resistant biofilm-forming

Acinetobacter baumannii. Scientific Reports. 2022;12(1):19869. DOI: https://doi.org/10.1038/s41598-022-24303-5
17. Kim I, Viswanathan K, Kasi G, Thanakkasaranee S, Sadeghi K, Seo J. ZnO Nanostructures in Active Antibacterial Food Packaging: Preparation Methods, Antimicrobial Mechanisms, Safety Issues, Future Prospects, and Challenges. Food Reviews International. 2020;38:537–565. DOI: https://doi.org/10.1080/87559129.2020.1737709
18. Luengo Morato Y, Ovejero Paredes K, Lozano Chamizo L, Marciello M, Filice M. Recent Advances in Multimodal Molecular Imaging of Cancer Mediated by Hybrid Magnetic NPs. Polymers (Basel). 2021;13(17):2989. DOI: https://doi.org/10.3390/polym13172989
19. Kim J, Lee N, Hyeon T. Recent development of NPs for molecular imaging. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences. 2017;375(2107):20170022. DOI: https://doi.org/10.1098/rsta.2017.0022
20. Jokerst JV, Gambhir SS. Molecular imaging with theranostic NPs. Accounts of Chemical Research. 2011;44(10):1050-1060. DOI: https://pubs.acs.org/doi/abs/10.1021/ar200106e
21. Mahmoud K, Swidan S, El-Nabarawi M, Teaima M. Lipid based NPs as a novel treatment modality for hepatocellular carcinoma: a comprehensive review on targeting and recent advances. Journal of Nanobiotechnology. 2022;20(1):109. DOI: https://doi.org/10.1186/s12951-022-01309-9
22. Panda S, Suryawanshi M. Fabrication, Characterization and Toxicity Evaluation Chemically Cross Linked Polymeric Material: A Proof of Concept. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN). 2023;16(3):6522-6532. DOI: https://doi.org/10.37285/ijpsn.2023.16.3.6
23. Li Y, Miao Y, Chen M, *et al*. Stepwise targeting and responsive lipid-coated NPs for enhanced tumor cell sensitivity and hepatocellular carcinoma therapy. Theranostics. 2020;10(8):3722-3736. DOI: https://doi.org/10.7150%2Fthno.42008
24. Palani N, Vijayakumar P, Monisha P, Ayyadurai S, Rajadesingu S. Electrospun nanofibers synthesized from polymers incorporated with bioactive compounds for wound healing. Journal of Nanobiotechnology. 2024;22(1):211. DOI: https://doi.org/10.1186/s12951-024-02491-8
25. Bai Q, Han K, Dong K, Zheng C, Zhang Y, Long Q, Lu T. Potential applications of nanomaterials and technology for diabetic wound healing. International journal of nanomedicine. 2020;9717-9743. DOI: https://doi.org/10.2147/IJN.S276001
26. Chen S, Wang Y, Bao S, Yao L, Fu X, Yu Y, Lyu H, Pang H, Guo S, Zhang H, Zhou P. Cerium oxide NPs in wound care: a review of mechanisms and therapeutic applications. Frontiers in Bioengineering and Biotechnology. 2024;12:1404651. DOI: https://doi.org/10.3389/fbioe.2024.1404651
27. Alharbi HM. Exploring the Frontier of Biopolymer-Assisted Drug Delivery: Advancements, Clinical Applications, and Future Perspectives in Cancer Nanomedicine. Drug Design, Development and Therapy. 2024;18:2063. DOI: https://doi.org/10.2147%2FDDDT.S441325
28. Bai Y, Wang Z, Liu D, Meng X, Wang H, Yu M, Zhang S, Sun T. Enhancing Ovarian Cancer Treatment with Maleimide-Modified Pt (IV) Prodrug NPs. Materials Today Bio. 2024:101131. DOI: https://doi.org/10.1016/j.mtbio.2024.101131
29. Thang NH, Chien TB, Cuong DX. Polymer-Based Hydrogels Applied in Drug Delivery: An Overview. Gels. 2023;9(7):523. DOI: https://doi.org/10.3390/gels9070523
30. Mondal A, Nayak AK, Chakraborty P, Banerjee S, Nandy BC. Natural Polymeric Nanobiocomposites for Anti-Cancer Drug Delivery Therapeutics: A Recent Update. Pharmaceutics. 2023;15(8):2064. DOI: https://doi.org/10.3390/pharmaceutics15082064
31. Butenko S, Miwa H, Liu Y, Plikus MV, Scumpia PO, Liu WF. Engineering immunomodulatory biomaterials to drive skin wounds toward regenerative healing. Cold Spring Harbor Perspectives in Biology. 2023;15(5):a041242. DOI: https://cshperspectives.cshlp.org/content/15/5/a041242.short
32. Li YY, Ji SF, Fu XB, Jiang YF, Sun XY. Biomaterial-based mechanical regulation facilitates scarless wound healing with functional skin appendage regeneration. Military Medical Research. 2024;11(1):13. DOI: https://doi.org/10.1186/s40779-024-00519-6
33. Bottini M, Bottini N. Modified carbon nanotubes: from nanomedicine to nanotoxicology. InCarbon Nanotubes, Graphene, and Associated Devices. 2012;8462. DOI: https://doi.org/10.1117/12.931232
34. Madgula K, Peddada LM, Pattathil SD. Chapter 3 - Biologically synthesized nanocarriers for TDDS applications. In: Nanotechnology for Drug Delivery and Pharmaceuticals. Academic Press. 2023:43-70. DOI: https://doi.org/10.1016/B978-0-323-95325-2.00009-2
35. Willis L, Hayes D, Mansour HM. Therapeutic liposomal dry powder inhalation aerosols for targeted lung delivery. Lung. 2012;190:251-262. DOI: https://doi.org/10.1007/s00408-011-9360-x
36. Pandolfi L, Ferrari M, Minardi S, Tasciotti E, Liu X, Taraballi F. Composite microsphere-functionalized scaffold for the controlled release of small molecules in tissue engineering. Journal of Tissue Engineering. 2016;7:204173141562466. DOI: https://doi.org/10.1177/2041731415624668
37. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision NPs for drug delivery. Nature reviews drug discovery. 2021;20(2):101-24. DOI: https://doi.org/10.1038/s41573-020-0090-8
38. Yaari Z, Da Silva D, Zinger A, Goldman E, Kajal A, Tshuva R, Barak E, Dahan N, Hershkovitz D, Goldfeder M, Roitman JS. Theranostic barcoded NPs for personalized cancer medicine. Nature communications. 2016;7(1):13325. DOI: https://doi.org/10.1038/ncomms13325
39. Sau S, Tatiparti K, Alsaab HO, Kashaw SK, Iyer AK. A tumor multicomponent targeting chemoimmune drug delivery system for reprograming the tumor microenvironment and personalized cancer therapy. Drug Discovery Today. 2018;23(7):1344-1356. DOI: https://doi.org/10.1016/j.drudis.2018.03.003
40. Qu F, Geng R, Liu Y, Zhu J. Advanced nanocarrier- and microneedle-based transdermal drug delivery strategies for skin diseases treatment. Theranostics. 2022;12(7):3372-3406. DOI: https://doi.org/10.7150%2Fthno.69999
41. Alshawwa SZ, Kassem AA, Farid RM, Mostafa SK, Labib GS. Nanocarrier Drug Delivery Systems: Characterization, Limitations, Future Perspectives and Implementation of Artificial Intelligence. Pharmaceutics. 2022;14(4):883. DOI: https://doi.org/10.3390/pharmaceutics14040883
42. Mi P. Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics. Theranostics. 2020;10(10):4557-4588. DOI: https://doi.org/10.7150%2Fthno.38069

43. Gote V, Nookala AR, Bolla PK, Pal D. Drug resistance in metastatic breast cancer: tumor targeted nanomedicine to the rescue. International journal of molecular sciences. 2021;22(9):4673. DOI: https://doi.org/10.3390/ijms22094673
44. Sun X, Zhao P, Lin J, Chen K, Shen J. Recent advances in access to overcome cancer drug resistance by nanocarrier drug delivery system. Cancer Drug Resistance. 2023;6(2):390. DOI: https://doi.org/10.20517%2Fcdr.2023.16
45. Talib WH, Alsayed AR, Barakat M, Abu-Taha MI, Mahmod AI. Targeting Drug Chemo-Resistance in Cancer Using Natural Products. Biomedicines. 2021;9(10):1353. DOI: https://doi.org/10.3390/biomedicines9101353
46. Yadav P, Ambudkar SV, Rajendra Prasad N. Emerging nanotechnology-based therapeutics to combat multidrug-resistant cancer. Journal of Nanobiotechnology. 2022;20(1):423. DOI: https://doi.org/10.1186/s12951-022-01626-z
47. Liu Y, Wang Y, Zhang J, *et al*. Nanotherapeutics targeting autophagy regulation for improved cancer therapy. Acta Pharmaceutica Sinica B. 2024;14(6):2447-2474. DOI: https://doi.org/10.1016/j.apsb.2024.03.019
48. Timon-David E, Perez C, Rodallec A. Nanotherapeutics Plus Immunotherapy in Oncology: Who Brings What to the Table?. Pharmaceutics. 2022;14(11):2326. DOI: https://doi.org/10.3390/pharmaceutics14112326
49. Wei X, Song M, Jiang G, *et al*. Progress in advanced nanotherapeutics for enhanced photodynamic immunotherapy of tumor. Theranostics. 2022;12(12):5272-5298. DOI: https://doi.org/10.7150%2Fthno.73566
50. Kumari A, Kaur A, Aggarwal G. The emerging potential of siRNA nanotherapeutics in treatment of arthritis. Asian Journal of Pharmaceutical Sciences. 2023;18(5):100845. DOI: https://doi.org/10.1016/j.ajps.2023.100845
51. Chehelgerdi M, Chehelgerdi M, Allela OQ, Pecho RD, Jayasankar N, Rao DP, Thamaraikani T, Vasanthan M, Viktor P, Lakshmaiya N, Saadh MJ. Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. Molecular cancer. 2023;22(1):169. DOI: https://doi.org/10.1186/s12943-023-01865-0
52. Sarkar S, Osama K, Mohammad Sajid Jamal Q, Amjad Kamal M, Sayeed U, Khan KA, Siddiqui H, Akhtar S. Advances and implications in nanotechnology for lung cancer management. Current drug metabolism. 2017;18(1):30-38. DOI: https://www.ingentaconnect.com/content/ben/cdm/2017/00000018/00000001/art00008
53. Dreaden EC, El-Sayed MA. Detecting and destroying cancer cells in more than one way with noble metals and different confinement properties on the nanoscale. Nanomaterials and Neoplasms. 2021:1-29. DOI: 9780429027819
54. Coelho SC, Pereira MC, Juzeniene A, Juzenas P, Coelho MA. Supramolecular nanoscale assemblies for cancer diagnosis and therapy. Journal of Controlled Release. 2015;213:152-167. DOI: https://doi.org/10.1016/j.jconrel.2015.06.034
55. Salvioni L, Rizzuto MA, Bertolini JA, Pandolfi L, Colombo M, Prosperi D. Thirty Years of Cancer Nanomedicine: Success, Frustration, and Hope. Cancers (Basel). 2019;11(12):1855. DOI: https://doi.org/10.3390/cancers11121855
56. Paus C, van der Voort R, Cambi A. Nanomedicine in cancer therapy: Promises and hurdles of polymeric NPs. Exploration of Medicine. 2021;2(2):167-185.DOI: https://doi.org/10.37349/emed.2021.00040
57. Sudheesh MS, Pavithran K, Sabitha M. Revisiting the outstanding questions in cancer nanomedicine with a future outlook. Nanoscale Advances. 2022;4(3):634-653. DOI: https://doi.org/10.1039/D1NA00810B
58. Yang C, Merlin D. Challenges to Safe Nanomedicine Treatment. Nanomaterials (Basel). 2023;13(7):1171. DOI: https://doi.org/10.3390/nano13071171
59. Rasool M, Malik A, Waquar S, *et al*. New challenges in the use of nanomedicine in cancer therapy. Bioengineered. 2022;13(1):759-773. DOI: https://doi.org/10.1080/21655979.2021.2012907
60. Metselaar JM, Lammers T. Challenges in nanomedicine clinical translation. Drug delivery and translational research. 2020;10:721-725. DOI: https://doi.org/10.1007/s13346-020-00740-5
61. Ragelle H, Danhier F, Préat V, Langer R, Anderson D G. (). Nanoparticle-based drug delivery systems: a commercial and regulatory outlook as the field matures. Expert Opinion on Drug Delivery, 2016;14(7):851–864. DOI: https://doi.org/10.1080/17425247.2016.1244187
62. Malik S, Muhammad K, Waheed Y. Nanotechnology: A Revolution in Modern Industry. Molecules. 2023;28(2):661. DOI: https://doi.org/10.3390/molecules28020661
63. Ashraf SA, Siddiqui AJ, Abd Elmoneim OE, Khan MI, Patel M, Alreshidi M, Moin A, Singh R, Snoussi M, Adnan M. Innovations in nanoscience for the sustainable development of food and agriculture with implications on health and environment. Science of the Total Environment. 2021;768:144990. DOI: https://doi.org/10.1016/j.scitotenv.2021.144990
64. Rambaran T, Schirhagl R. Nanotechnology from lab to industry–a look at current trends. Nanoscale advances. 2022;4(18):3664-3675. DOI: https://doi.org/10.1039/D2NA00439A
65. Hemlata, Meena PR, Singh AP, Tejavath KK. Biosynthesis of Silver NPs Using Cucumis prophetarum Aqueous Leaf Extract and Their Antibacterial and Antiproliferative Activity Against Cancer Cell Lines. ACS Omega. 2020;5(10):5520-5528. DOI: https://pubs.acs.org/doi/full/10.1021/acsomega.0c00155
66. Akhatova F, Konnova S, Kryuchkova M, Batasheva S, Mazurova K, Vikulina A, Volodkin D, Rozhina E. Comparative Characterization of Iron and Silver NPs: Extract-Stabilized and Classical Synthesis Methods. International Journal of Molecular Sciences. 2023;24(11):9274. DOI: https://doi.org/10.3390/ijms24119274
67. Mourdikoudis S, Pallares RM, Thanh NTK. Characterization Techniques for NPs: Comparison and Complementarity upon Studying Nanoparticle Properties. Nanoscale. 2018;10:12871-12934. DOI: https://doi.org/10.1039/C8NR02278J
68. Rodriguez-Loya J, Lerma M, Gardea-Torresdey JL. Dynamic Light Scattering and Its Application to Control Nanoparticle Aggregation in Colloidal Systems: A Review. Micromachines (Basel). 2023;15(1):24. DOI: https://doi.org/10.3390/mi15010024
69. Maguire CM, Rösslein M, Wick P, Prina-Mello A. Characterisation of particles in solution–a perspective on light scattering and comparative technologies. Science and technology of advanced materials. 2018;19(1):732-745. DOI: https://doi.org/10.1080/14686996.2018.1517587
70. Bhattacharjee S. DLS and ZP–what they are and what they are not?. Journal of controlled release. 2016;235:337-351. DOI: https://doi.org/10.1016/j.jconrel.2016.06.017
71. Malatesta M. Transmission electron microscopy as a powerful tool to investigate the interaction of NPs with subcellular structures. International Journal of Molecular Sciences.

2021;22(23):12789. DOI: https://doi.org/10.3390/ijms222312789
72. Fuentes-Cervantes A, Ruiz Allica J, Calderón Celis F, Costa-Fernández JM, Ruiz Encinar J. The Potential of ICP-MS as a Complementary Tool in Nanoparticle-Protein Corona Analysis. Nanomaterials (Basel). 2023;13(6):1132. DOI: https://doi.org/10.3390/nano13061132
73. Wang X, Cao Y. Characterizations of absorption, scattering, and transmission of typical NPs and their suspensions. Journal of Industrial and Engineering Chemistry. 2020;82:324-332. DOI: https://doi.org/10.1016/j.jiec.2019.10.030
74. Hng HP. Investigation of green synthesized silver nanoaprticles using aqueous leaf extract of Artemisia Argyi for antioxidant and antimicrobial potentials. International Journal of Pharmaceutical Quality Assurance 2017;8(4);190-199. DOI: 10.25258/ijpqa.v8i04.10545
75. Lata S, Mittal SK. Identification of flavonoid glycosides of methanol extract from cucumis dipsaceus ehrenb.(fruit) by using HPLC-UV-ESI-MS methods. International Journal of Pharmaceutical Quality Assurance 2017;8(4);183-189 DOI: 10.25258/ijpqa.v8i04.10544
76. Kujur A, Daharwal SJ. Box–Behnken Design Based Optimization of Process Variables for the Green Synthesis of 18-Beta–Glycyrrhetinic Acid Silver NPs and Evaluation of its Antioxidant, Antimicrobial Activity. International Journal of Drug Delivery Technology. 2023;13(2):501-509. DOI: 10.25258/ijddt.13.2.08
77. Aljeboree AM, Radia ND, Kadam ZM, Faleh YA, Altimari US, Dawood AH, Alkaim AF. Study on Control-release and Synchronized of Metformin Hydrochloride Drug from Hydrophilic Polymers AgNP/SCC-g-poly (AAcAAm). International Journal of Drug Delivery Technology. 2023;13(2):708-712. DOI: 10.25258/ijddt.13.2.38
78. Ibraheem SR, Al-Ogaidi I, Al-Azawi HF. Green Synthesis of Silver NPs via Black and Green Tea and Study its Toxicity on few Vital Organs of Female Mice. International Journal of Drug Delivery Technology. 2022;12(4):1537-1541. DOI: 10.25258/ijddt.12.4.09