



## Original Investigation | Neurology

# Alzheimer's Disease Frontiers: Nanotherapeutics, Gut Microbiota, and Future Directions: A Systematic Review

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### Key Points

#### Question:

How does gut microbiota affect Alzheimer's disease (AD)?  
Can nanotherapeutics improve AD treatment?  
What are future directions for AD therapies?

#### Findings:

Global AD prevalence is rising, with genetic factors like APOE  $\epsilon 4$  playing a major role. Gut microbiota dysregulation is linked to AD and may offer diagnostic and treatment potential. Nanotechnology (e.g., nanoliposomes, exosomes) shows promise in enhancing drug delivery.

#### Meaning:

Innovative approaches like nanotechnology and microbiota-based therapies are crucial to address the limitations of current AD treatments.

### Abstract

#### Importance:

Alzheimer's disease (AD) is a progressive neurodegenerative disease with no cure, causing apathy, mood and neuropsychiatric issues, and cognitive impairment.

#### Objective:

This study focuses on understanding its pathophysiology and discovering new therapeutics. It also discusses the development of nanotherapeutic techniques, which incorporate nanomaterials that pass across the blood-brain barrier and function as therapeutic mechanisms.

#### Evidence Review:

A systematic search of PubMed and google scholar for studies such as randomized control trials, reviews and systematic reviews published in the past 5 years. Key words used are AD, gut microbiota, nanotechnology in AD were used.

#### Findings:

The global dementia prevalence is increasing, with heritable factors influencing AD risk by 60-80%. The prevalence of Alzheimer's will double in Europe and triple in other countries by 2050. Gut microbiota dysregulation is linked to AD pathogenesis, and correcting gut microbiota eubiosis may be a diagnostic tool. Novel biomarkers, pharmacological methods, stem cell-based treatment, nanotechnology, and lifestyle-based preventative studies are being investigated for AD treatment. The APOE  $\epsilon 4$  allele is a significant genetic risk factor for sporadic AD, and various treatment methods have proven effective in mouse models. Advancements in gene therapy, immunotherapy, peptidomimetics, metal chelators, and probiotics are also being explored. Nanoliposomes and exosomes are being explored as innovative approaches.

#### Conclusions and Relevance:

Nanotechnology advancements are transforming drug delivery systems, targeting multiple therapeutic moieties and improving bioavailability and penetration across the central nervous system. Current therapies struggle to produce good results or stop disease progression. Gut microbiome changes have been linked to neurodegeneration, opening new microbiota-based treatment alternatives. More study is needed to investigate these therapies and other techniques like stem cell therapy and nanotechnology. The FDA has only authorized aducanumab since 2003, emphasizing the need for new pharmaceutical techniques to combat Alzheimer's disease.

## References

- Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C. E., Cummings, J., & van der Flier, W. M. (2021). Alzheimer's disease. *Lancet (London, England)*, 397(10284), 1577–1590. [https://doi.org/10.1016/S0140-6736\(20\)32205-4](https://doi.org/10.1016/S0140-6736(20)32205-4)
- Khan, S., Barve, K. H., & Kumar, M. S. (2020). Recent Advancements in Pathogenesis, Diagnostics and Treatment of Alzheimer's Disease. *Current neuropharmacology*, 18(11), 1106–1125. <https://doi.org/10.2174/1570159X18666200528142429>
- Breijyeh, Z., & Karaman, R. (2020). Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules (Basel, Switzerland)*, 25(24), 5789. <https://doi.org/10.3390/molecules25245789>
- Passeri, E., Elkhoury, K., Morsink, M., Broersen, K., Linder, M., Tamayol, A., Malaplate, C., Yen, F. T., & Arab-Tehrany, E. (2022). Alzheimer's Disease: Treatment Strategies and Their Limitations. *International journal of molecular sciences*, 23(22), 13954. <https://doi.org/10.3390/ijms232213954>
- Serrano-Pozo, A., Das, S., & Hyman, B. T. (2021). APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. *The Lancet. Neurology*, 20(1), 68–80. [https://doi.org/10.1016/S1474-4422\(20\)30412-9](https://doi.org/10.1016/S1474-4422(20)30412-9)
- Stefaniak, O., Dobrzyńska, M., Drzymała-Czyż, S., & Przystawski, J. (2022). Diet in the Prevention of Alzheimer's Disease: Current Knowledge and Future Research Requirements. *Nutrients*, 14(21), 4564. <https://doi.org/10.3390/nu14214564>
- Monteiro, A. R., Barbosa, D. J., Remião, F., & Silva, R. (2023). Alzheimer's disease: Insights and new prospects in disease pathophysiology, biomarkers and disease-modifying drugs. *Biochemical pharmacology*, 211, 115522. <https://doi.org/10.1016/j.bcp.2023.115522>
- Yu, T. W., Lane, H. Y., & Lin, C. H. (2021). Novel Therapeutic Approaches for Alzheimer's Disease: An Updated Review. *International journal of molecular sciences*, 22(15), 8208. <https://doi.org/10.3390/ijms22158208>
- Athar, T., Al Balushi, K., & Khan, S. A. (2021). Recent advances on drug development and emerging therapeutic agents for Alzheimer's disease. *Molecular biology reports*, 48(7), 5629–5645. <https://doi.org/10.1007/s11033-021-06512-9>
- Faiyaz, M., Ganayee, M. A., Akhtar, S., Krishnan, S., Flora, B., Dogra, D., Jha, N. K., Chellappan, D. K., Negi, P., Dua, K., Kesari, K. K., & Gupta, P. K. (2021). Nanomaterials in Alzheimer's disease treatment: a comprehensive review. *Frontiers in bioscience (Landmark edition)*, 26(10), 851–865. <https://doi.org/10.52586/4992>
- Srivastava, S., Ahmad, R., & Khare, S. K. (2021). Alzheimer's disease and its treatment by different approaches: A review. *European journal of medicinal chemistry*, 216, 113320. <https://doi.org/10.1016/j.ejmech.2021.113320>
- Guzman-Martinez, L., Calfio, C., Farias, G. A., Vilches, C., Prieto, R., & Maccioni, R. B. (2021). New Frontiers in the Prevention, Diagnosis, and Treatment of Alzheimer's Disease. *Journal of Alzheimer's disease : JAD*, 82(s1), S51–S63. <https://doi.org/10.3233/JAD-201059>

## References (Continues..)

- Yu, T. W., Lane, H. Y., & Lin, C. H. (2021). Novel Therapeutic Approaches for Alzheimer's Disease: An Updated Review. *International journal of molecular sciences*, 22(15), 8208. <https://doi.org/10.3390/ijms22158208>
- Wang, Z. B., Wang, Z. T., Sun, Y., Tan, L., & Yu, J. T. (2022). The future of stem cell therapies of Alzheimer's disease. *Ageing research reviews*, 80, 101655. <https://doi.org/10.1016/j.arr.2022.101655>
- Faiyaz, M., Ganayee, M. A., Akhtar, S., Krishnan, S., Flora, B., Dogra, D., Jha, N. K., Chellappan, D. K., Negi, P., Dua, K., Kesari, K. K., & Gupta, P. K. (2021). Nanomaterials in Alzheimer's disease treatment: a comprehensive review. *Frontiers in bioscience (Landmark edition)*, 26(10), 851–865. <https://doi.org/10.52586/4992>
- Li, L., Zhang, J., Huang, X., Du, J., Tu, Z., Wu, H., Liu, X., & Yuan, M. (2023). Research Progress of Nanocarriers for the Treatment of Alzheimer's Disease. *Current pharmaceutical design*, 29(2), 95–115. <https://doi.org/10.2174/1381612829666221216114912>
- Fonseca, L. C., Lopes, J. A., Vieira, J., Viegas, C., Oliveira, C. S., Hartmann, R. P., & Fonte, P. (2021). Intranasal drug delivery for treatment of Alzheimer's disease. *Drug delivery and translational research*, 11(2), 411–425. <https://doi.org/10.1007/s13346-021-00940-7>
- Dogra, A., Narang, R. S., & Narang, J. K. (2020). Recent Advances in Nanotherapeutic Interventions for the Treatment of Alzheimer's Disease. *Current pharmaceutical design*, 26(19), 2257–2279. <https://doi.org/10.2174/1381612826666200422092620>
- Salwa, & Kumar, L. (2021). Engrafted stem cell therapy for Alzheimer's disease: A promising treatment strategy with clinical outcome. *Journal of controlled release : official journal of the Controlled Release Society*, 338, 837–857. <https://doi.org/10.1016/j.jconrel.2021.09.007>
- Binda, A., Murano, C., & Rivolta, I. (2020). Innovative Therapies and Nanomedicine Applications for the Treatment of Alzheimer's Disease: A State-of-the-Art (2017-2020). *International journal of nanomedicine*, 15, 6113–6135. <https://doi.org/10.2147/IJN.S231480>

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