DOI: 10.21088/ijnns.0975.0223.17225.3

International Journal of Neurology and Neurosurgery
Volume 17, Number 2 May-August 2025

REVIEW ARTICLE

Advanced Computational Approaches for ADME Evaluation of Neurological Disorders

Ankita Singh[1], Prachi Srivastava[2]

HOW TO CITE THIS ARTICLE:

Ankita Singh, Prachi Srivastava. Advanced Computational Approaches for ADME Evaluation of Neurological Disorders. International Journal of Neurology and Neurosurgery. 2025; 17(2): 80-87.

ABSTRACT

The effectiveness of any drug centers majorly on its pharmacokinetic features, such as the 'absorption', 'distribution', 'metabolism', and 'excretion' of the drug [ADME]. The Complexities in drug development for disorders like epilepsy, Alzheimer's disease, and Parkinson's disease, are posed due to presence of neuro-physiological features, like the blood-brain barrier [BBB]. Most experimental and computational approaches lack precision in describing drug activity at the atomic level, especially the intricate electronic interactions that dictate their actions. Additive QM techniques significantly enhance the precision of ADME estimates because the calculation of electronic structure, molecular interaction, and reaction mechanisms is correct. This review looks into where and how the rational drug design and synthesis of QM models in silico facilitates the ADME assessment and process of creating drugs for the nervous system. Special focus is given to the DFT application for The molecular stability and reactivity EM of the modified ADME, quantum enhanced molecular docking to the BBB permeability, and quantum mechanics descriptors for QSAR models. Further, we cover the blended QM/MM simulations together with other artificial intelligence methods. Through these advanced computational tools, researchers are able to develop more effective neurotherapies with better drug metabolism and lower toxicity risk which expedites the drug discovery process.

KEYWORDS

• Neurological disorders • ADME Prediction • Blood-Brain Barrier • Computational drug design • Quantum mechanics

AUTHOR'S AFFILIATION:

[1] Department of Bioinformatics, Amity Institute of Biotechnology, Amity University, Lucknow, Uttar Pradesh, India.

[2] Associate Professor, Department of Bioinformatics, Amity Institute of Biotechnology, Amity University, Lucknow, Uttar Pradesh, India.

CORRESPONDING AUTHOR:

Prachi Srivastava, Associate Professor, Department of Bioinformatics, Amity Institute of Biotechnology, Amity University, Lucknow, Uttar Pradesh, India.

E-mail: psrivastava@amity.edu

➢ **Received:** 13-03-2025 ➢ **Accepted:** 26-04-2025

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) *which permits non-Commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the Red Flower Publication and Open Access pages* (https://www.rfppl.co.in)

Key messages: Drug efficacy highly depends on the ADME properties, with the neurological drug development facing hindrances due to the blood brain barrier [BBB]. The Traditional computational methods mostly lack precision in modelling drug interactions at atomic-level, whereas the quantum mechanics [QM] enhances the ADME predictions via electronic structure analysis, quantum docking, density functional theory [DFT], and QSAR modelling. The integration of the QM/MM simulations along with artificial intelligence improves the metabolism prediction of drug, optimizing the neurotherapy development by enhancement of efficacy and reduction of toxicity risks.

INTRODUCTION

Neurological disorders like Epilepsy, Alzheimer's disease (AD), and Parkinson's disease (PD) pose major public health challenges, affecting millions globally. Chronic pain, arising from CNS injury and neuroinflammation, impacts 20–40% of patients and is now considered a brain diseases.[1] Despite CNS disease burdens, drug translation from animal models to humans remains complex due to pharmacokinetic/ pharmacodynamics (PKPD) challenges. BBB plays a crucial role in neurological drug development.[2] Computational drug design, including structure-based (SBDD) and ligand-based (LBDD) approaches, refines drug discovery.[3] Quantum biology explores non-classical effects in biological processes.[4]

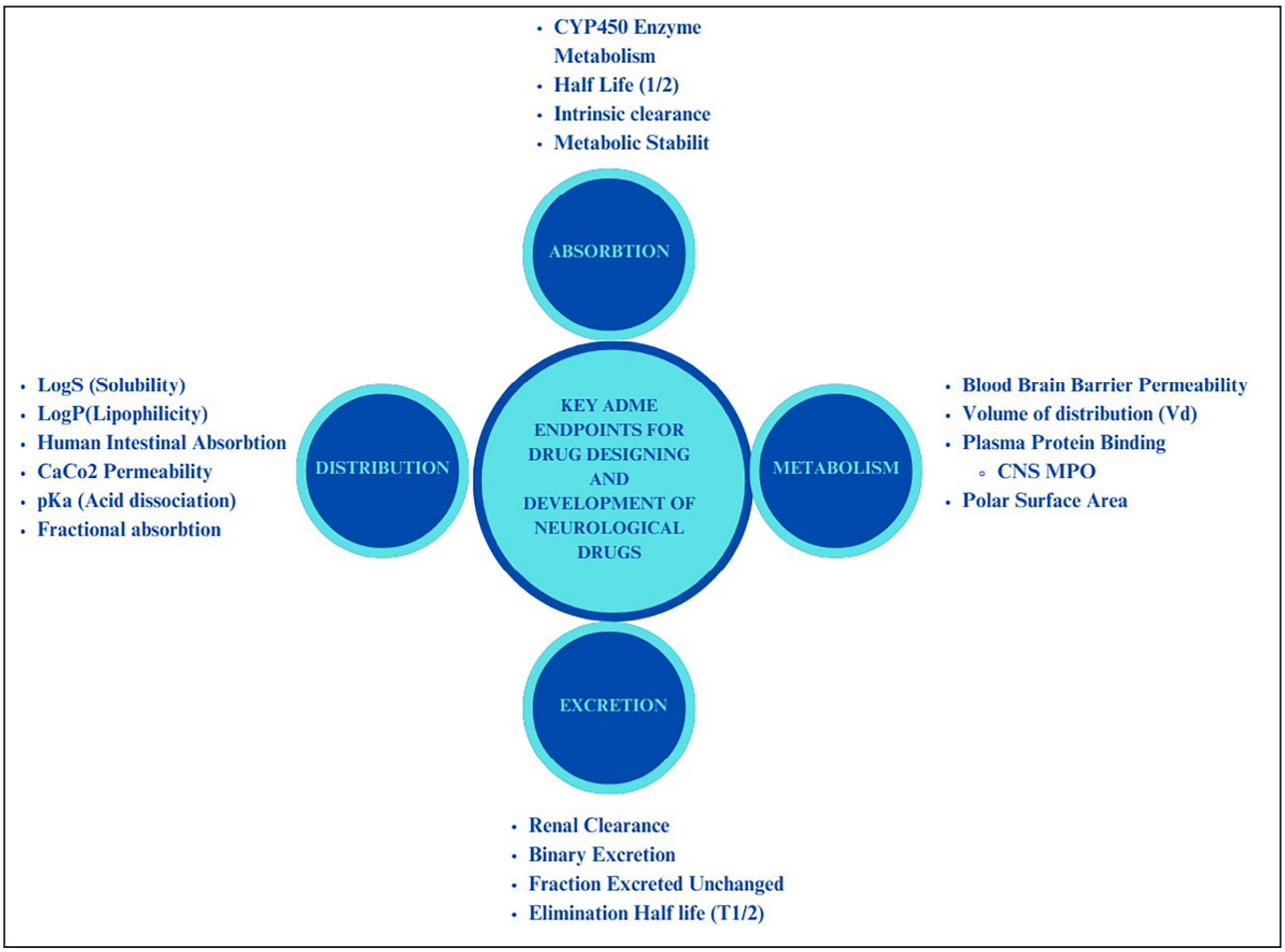


Figure 1: Graphical representation of Key ADME endpoints for Drug Designing and Development of Neurological drugs

REVIEW OF LITERATURE

Neurological Disorders:

The neuropathic pain arises from damages occurred in the central nervous system [CNS] or peripheral nervous system, leading to halted brain activity in the neurological diseases. The chronic pain is now regarded as a brain disease due to anatomical, functional, and chemical changes in the modulatory, sensory, and emotional brain systems.[5,6] Neuro-imaging has identified various activation states associated with pain.[7] Different genetic studies have identified various pain-protective markers, like GCH1, CACNG2, and KCNS1which influence the susceptibility towards chronic pain.[8,9,10] The Genome-wide analysis [GWAS] studies may further refine the genetic predictors of pain [11]. Understanding of genetic and neuro-biological links between neurological condition scan facilitate the targeted interventions.[12,13]

Important ADME parameters for neurological drug:

The key **ADME [Absorption, Distribution, Metabolism, and Excretion]** parameters influence their safety and efficacy. The **Absorption** depends on 'lipophilicity' [LogP ~1–3] for blood-brain barrier [BBB] penetration, the 'permeability' [>10 × 10^{-6} cm/s in 'Caco-2/MDCK' assays], and ionization [pKa ~7–9]. **Distribution of drug** requires very high BBB permeability [LogBB > 0.3], moderate 'volume of distribution' [~0.5–3 L/kg], and <95% 'plasma protein binding' for optimal brain exposure. The **Metabolism** is primarily mediated through CYP enzymes [CYP3A4, CYP2D6], affecting the half-life [~4–12 hours] and drug clearance. The **Excretion** should involve the hepatic metabolism over the renal elimination to prevent toxicity, with the 'clearance' ranging from '0.1–1 mL/min/kg'. The **Special considerations** includes the efflux transporter interactions [P-gp, BCRP], as inhibiting these transporters improves brain penetration as well as brain exposure metrics [Kp,uu > 0.1] for the effective CNS targeting. The Optimization of these parameters ensures better drug bioavailability, reduced systemic side effects, and sustained action.[14]

Blood Brain Barrier mechanisms as important Parameter:

The blood brain barrier [BBB] is a highly specialized structure which regulates the exchange of molecules between the central nervous system [CNS] and blood.[15,16] The endothelial cells [ECs] form the core of Blood Brain Barrier, supported by neuro-vascular unit [NVU].[17] The tight junctions [TJs] are made of proteins such as occludin and claudin-5 [CLDN5], which restrict para-cellular permeability.[18,19] Extracellular membrane of Central Nervous System exhibit low trans-cellular permeability because of limited caveolin mediated transcytosis, which is regulated by MFSD2A.[20,21] The Efflux transporters like MDR1/P-glycoprotein [PGP] prevent accumulation of toxins.[22,23] Solute transporters like LAT1 and GLUT1 facilitate the nutrient passage.[24,25] The leukocyte adhesion molecules are down regulated in Central Nervous System ECs, reducing the immune cell infiltration.[26,27] Hence, understanding of Blood Brain Barrier mechanisms is crucial for neurological disease research.

Challenges in Drug Development of Neurological Drugs:

Neurological disorders, considering all types, affect more than 1 billion people across the world.[28] In 2010, these conditions accounted for 30% of all the years lived with a disability [YLD].[29] However, the CNS drug development yet remains highly challenging, with a very low clinical approval rate [6% to 13%] and a very long market entry time [12 years or least 6–7 years] when compared to non-CNS drugs.[30,31,32] Animal models frequently fail to accurately predict the human CNS disorders because of differences in the blood brain barrier permeabilities, transporter mechanisms and metabolism.[33,34,35] To address these challenges, in-silico modeling, human pharmacokinetic assessments through the in-vitro systems, and the translational studies, are crucial.

Computer aided drug design

The Computer aided drug design [CADD] is classified into structure based and ligand based methods. In structure based methods, the 3D structure of the biological targets to assess the ligand binding potential. The Ligand based approach analyzes the structure activity relationships [SARs] from previously known active and inactive compounds to predict the new drug candidates. The challenge actually lies in accurate description of chemical structures using 3D or 2D descriptors. Both methods score the molecules based on

molecular properties, similarity, or binding energy. These approaches are often combined for improved efficiency and accuracy, making them highly essential for the early stage drug discovery and identification of the new chemical entities.[36]

Quantum mechanics approaches

The quantum physics has been speculated to influence the biological processes, precisely human consciousness and evolution, even if it lacks experimental validation.[37,38] It is proposed that microtubules function as the quantum bits, enabling the complex computation through the quantum coherence, with consciousness emerging from the collapse of gravity induced wave function. But, no experiments confirm the stablility of macroscopic quantum superpositions in the biology, and the de-coherence timescales[39,40] are too short. It was suggested that quantum mechanics accelerate evolution,[41] but de-coherence studies[42] challenge this. Despite being speculative, these ideas inspires an interdisciplinary research in quantum biology and the consciousness studies.

Tools used in ADME Evaluation of Drugs

Table 1: Tools for ADME Evaluation and Quantum mechanic analysis

Tool Name	Endpoints	Uses	Reference
SwissADME	logS [-10 to 0], logP [-3 to +6], BBB Penetration [Yes/No], GI Absorption [High/Low]	Predicts ADME Properties like, lipophilicity, solubility, and other pharmacokinetics	43
pkCSM	Human Intestinal Absorption (HIA) [0–100%], logS [-8 to 1], logP [-3 to +8], VDss [Low/High]	Predicts ADME properties using graph-based signatures	44
ADMET Predictor	logP (-5 to +10), logS (-12 to 2), CYP450 Inhibition (Yes/No), Plasma Protein Binding (0–100%)	Predicts ADME and toxicity profiles using QSAR models	45
PreADMET	logS [-10 to 1], logP [-5 to +8], BBB Permeability [logBB: -3 to +1],	Estimates the drug absorption, distribution, and metabolism	46
QikProp	logS [-9 to +1], logP [-4 to +6], Oral Bioavailability [L/H]	Predicts the ADME properties as well as drug-likeness based on molecular descriptors	47
GastroPlus	F [Fraction Absorbed: 0–1], Cmax [ng/mL: 1–1000], Tmax [0.5–12 h]	Simulates the absorption, distribution, metabolism, and elimination of drug	48
BOILED-Egg Model	logP [-3 to +6], GI Absorption [Yes/No], BBB Permeability	Predicts the BBB permeability and GI absorption using a graphical approach	49
Gaussian	Dipole Moment [0–10 D], Energy [Hartree: -1000 to 0], HOMO-LUMO Gap [eV: 0–10]	Performs the quantum chemistry calculations for the molecular properties and electronic structure	50
Q-Chem	HOMO-LUMO Gap [eV: 0–8], Vibrational Frequencies [cm^1: 0–4000], Dipole Moment [0–12 D],	Provides the molecular propertiessuch as energy, frequencies and charge distributions	51
ORCA	Total Energy [Hartree: -1500 to 0], Bond Length [Å: 0.5–3], Excitation Energy [eV: 0–10],	Performs the electronic structure calculations and the spectroscopic predictions	52
Spartan	Molecular Energy [Hartree: -2000 to 0], pKa [0–14], LogP [-5 to +5]	Performs the molecular modeling, structural optimization and energy calculations.	53
Jaguar	pKa [0–14], Dipole Moment [0–10 D], Reaction Energy [kcal/mol: -100 to +100]	Conducts the DFT calculations for drug-protein interactions and molecular reactivity.	54

METHODOLOGY

The study showcases an integrated computational approach for evaluation of ADME properties of the drugs used in treatment of neurological disorders. The study employ usage of various **ADME Prediction Tools**, like '**SwissADME', 'pkCSM', 'GastroPlus', and 'QikProp'**, estimates the **solubility [logS], lipophilicity [logP], blood-brain barrier [BBB] permeability, metabolism, and excretion [clearance]** to ensure suitability of the drug's pharmacokinetic properties for the neurological targets. The **Quantum Mechanics-Based Approaches** utilize the **Density Functional Theory [DFT]** to model the electronic properties like '**charge distribution',**

'HOMO-LUMO gap' , and 'dipole moment', which influence receptor interactions and drug permeability. The **Computer-Aided Drug Design [CADD]** methods, include **'Molecular docking', 'molecular dynamics [MD] simulations', and 'QSAR modeling',** which predict the drug efficacy by assessing the **'stability', 'binding affinity', and 'structural-activity relationships'**. Lastly, the '**Rational Drug Design'** which integrates computational predictions along with the '**lead optimization strategies'** to refine the drug candidates based on their **metabolic stability absorption, and bioavailability**, to improve CNS drug discovery and to reduce experimental failures. The availability of experimental validation further strengthens the computational findings.

CONCLUSION

The computational evaluation of ADME has become an integral part of drug discovery, to ensure whether the potential drug candidates exhibit desirable pharmacokinetic properties or not; The ADME properties such as 'efficient absorption', 'appropriate distribution', 'metabolic stability', and 'controlled excretion'. Neurological disorders require drugs which exhibit optimized blood brain barrier [BBB] permeability, less metabolic degradation, as well as minimal off target effects. The tools like Swiss ADME, Gastro Plus, pk CSM, and QikProp give quick as well as cost effective assessments of these properties. They enable early identification of the potential compounds while filtering out the unsuitable ones. This in-silico approach significantly accelerates drug development process by allowing researchers to predict drug behaviour in the body before conducting the labour intensive experimental studies.

The key ADME endpoints are very crucial in determination of effectiveness of a neurological drug. The absorption parameters such as human intestinal absorption [HIA] and logP [Lipophilicity] influence reach of drug in systemic circulation, while the distribution properties like the plasma protein binding [PPB] and logBB, which dictate how well the drug penetrates the Central Nervous System. In the drug Metabolism, interactions with the 'CYP450 enzymes' determines whether a drug remains active for a sufficient duration or not and excretory factors such as renal clearance [CL] and half life [T1/2] for ensuring proper elimination for avoidance of unnecessary accumulation and toxicity. The computational tools enhance the predictions via integration of multiple biological and physico-chemical factors, while the quantum mechanics-based methods like 'Density Functional Theory '[DFT] refine the molecular properties to improve the ADME accuracy.

The advancements in artificial intelligence [AI] and machine learning [ML] have enabled the precise models for ADME prediction, enabling the self-learning algorithms to continuously improve the models based on experimental data. The integration of , QM-based simulations, physiologically based pharmacokinetic [PBPK] modelling and AI driven optimization is expected to revolutionize the neurological drug discovery, leading to the safer and more effective therapies. Through incorporation of computational ADME evaluation early in the drug development, researchers are able to optimize drug candidates more efficiently hence reducing the failure rates in clinical trials and expediting development of innovative treatments for the neurological disorders.

Conflict of Interest: The authors declare no conflicts of interest related to this study.

REFERENCES

1. Borsook D. Neurological diseases and pain. Brain. 2012 Feb; 135(Pt 2): 320-44. doi: 10.1093/brain/awr271. Epub 2011 Nov 8. PMID: 22067541; PMCID: PMC3281476. https://pmc.ncbi.nlm.nih.gov/articles/PMC3281476/
2. Profaci C.P., Munji R.N., Pulido R.S., Daneman R. The blood-brain barrier in health and disease: Important unanswered questions. J Exp Med. 2020 Apr 6;217(4):e20190062. doi: 10.1084/jem.20190062. PMID: 32211826; PMCID: PMC7144528. https://pmc.ncbi.nlm.nih.gov/articles/PMC7144528/
3. Yu W., MacKerell AD Jr. Computer-Aided Drug Design Methods. Methods Mol Biol. 2017; 1520: 85-106. doi: 10.1007/978-1-4939-6634-9_5. PMID: 27873247; PMCID: PMC5248982. https://pmc.ncbi.nlm.nih.gov/articles/PMC5248982/
4. Arndt M., Juffmann T., Vedral V. Quantum physics meets biology. HFSP J. 2009 Dec; 3(6): 386-400. doi: 10.2976/1.3244985. Epub 2009 Nov 9. PMID: 20234806; PMCID: PMC2839811.

https://pmc.ncbi.nlm.nih.gov/articles/PMC2839811/#sec16

5. Moulton E.A., Schmahmann J.D., Becerra L., Borsook D. The cerebellum and pain: passive integrator or active participator? Brain Res Rev. 2010; 65: 14–27. doi: 10.1016/j.brainresrev.2010.05.005. [DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
6. Elman I, Zubieta JK, Borsook D. The missing p in psychiatric training: why it is important to teach pain to psychiatrists. Arch Gen Psychiatry. 2011;68:12–20. doi: 10.1001/archgenpsychiatry.2010.174. [DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
7. Tracey I., Mantyh P.W. The cerebral signature for pain perception and its modulation. Neuron. 2007; 55: 377–91. doi: 10.1016/j.neuron. 2007.07.012. [DOI] [PubMed] [Google Scholar][Ref list]
8. Tegeder I, Costigan M, Griffin RS, Abele A, Belfer I, Schmidt H, *et al*. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. Nat Med. 2006; 12: 1269–77. doi: 10.1038/nm1490. [DOI] [PubMed] [Google Scholar][Ref list]
9. Costigan M, Belfer I, Griffin RS, Dai F, Barrett LB, Coppola G, *et al*. Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. Brain. 2010; 133: 2519–27. doi: 10.1093/brain/awq195. [DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
10. Ni Z, Pinto AD, Lang AE, Chen R. Involvement of the cerebellothalamocortical pathway in Parkinson disease. Ann Neurol. 2010; 68: 816–24. doi: 10.1002/ana.22221. [DOI] [PubMed] [Google Scholar][Ref list]
11. Oertel B, Lotsch J. Genetic mutations that prevent pain: implications for future pain medication. Pharmacogenomics. 2008; 9: 179–94. doi: 10.2217/14622416.9.2.179. [DOI] [PubMed] [Google Scholar][Ref list]
12. Ren K., Dubner R. Interactions between the immune and nervous systems in pain. Nat Med. 2010; 6: 1267–76. doi: 10.1038/nm.2234. [DOI] [PMC free article] [PubMed] [Google Scholar][Ref list]
13. Austin P.J., Moalem-Taylor G. The neuro-immune balance in neuropathic pain: involvement of inflammatory immune cells, immune-like glial cells and cytokines. J Neuroimmunol. 2010; 229: 26–50. doi: 10.1016/j.jneuroim.2010.08.013. [DOI] [PubMed] [Google Scholar][Ref list]
14. Pajouhesh H, Lenz GR. Medicinal chemical properties of successful central nervous system drugs. NeuroRx. 2005 Oct;2(4):541-53. doi: 10.1602/neurorx.2.4.541. PMID: 16489364; PMCID: PMC1201314. https://pmc.ncbi.nlm.nih.gov/articles/PMC1201314/
15. Saunders N.R., Dziegielewska K.M., Unsicker K., and Ek C.J.. 2016. Delayed astrocytic contact with cerebral blood vessels in FGF-2 deficient mice does not compromise permeability properties at the developing blood-brain barrier. Dev. Neurobiol. 76:1201–1212. 10.1002/dneu.22383 [DOI] [PubMed] [Google Scholar]
16. Zlokovic B.V. 2008. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron. 57:178–201. 10.1016/j.neuron.2008.01.003 [DOI] [PubMed] [Google Scholar]
17. Obermeier B., Daneman R., and Ransohoff R.M.. 2013. Development, maintenance and disruption of the blood-brain barrier. Nat. Med. 19:1584–1596. 10.1038/nm.3407 [DOI] [PMC free article] [PubMed] [Google Scholar]
18. Amasheh S., Schmidt T., Mahn M., Florian P., Mankertz J., Tavalali S., Gitter A.H., Schulzke J.D., and Fromm M.. 2005. Contribution of claudin-5 to barrier properties in tight junctions of epithelial cells. Cell Tissue Res. 321:89–96. 10.1007/s00441-005-1101-0 [DOI] [PubMed] [Google Scholar]
19. Furuse M., Sasaki H., and Tsukita S.. 1999. Manner of interaction of heterogeneous claudin species within and between tight junction strands. J. Cell Biol. 147:891–903. 10.1083/jcb.147.4.891 [DOI] [PMC free article] [PubMed] [Google Scholar]
20. Ben-Zvi A., Lacoste B., Kur E., Andreone B.J., Mayshar Y., Yan H., and Gu C.. 2014. Mfsd2a is critical for the formation and function of the blood-brain barrier. Nature. 509:507–511. 10.1038/nature13324 [DOI] [PMC free article] [PubMed] [Google Scholar]
21. Nguyen L.N., Ma D., Shui G., Wong P., Cazenave-Gassiot A., Zhang X., Wenk M.R., Goh E.L., and Silver D.L.. 2014. Mfsd2a is a transporter for the essential omega-3 fatty acid docosahexaenoic acid. Nature. 509:503–506. 10.1038/nature13241 [DOI] [PubMed] [Google Scholar]
22. Shen S., and Zhang W.. 2010. ABC transporters and drug efflux at the blood-brain barrier. Rev. Neurosci. 21:29–53. 10.1515/REVNEURO.2010.21.1.29 [DOI] [PubMed] [Google Scholar]

23. Hindle S.J., Munji R.N., Dolghih E., Gaskins G., Orng S., Ishimoto H., Soung A., DeSalvo M., Kitamoto T., Keiser M.J., *et al*. 2017. Evolutionarily Conserved Roles for Blood-Brain Barrier Xenobiotic Transporters in Endogenous Steroid Partitioning and Behavior. Cell Rep. 21:1304–1316. 10.1016/j.celrep.2017.10.026 [DOI] [PMC free article] [PubMed] [Google Scholar]

24. Boado R.J., Li J.Y., Nagaya M., Zhang C., and Pardridge W.M.. 1999. Selective expression of the large neutral amino acid transporter at the blood-brain barrier. Proc. Natl. Acad. Sci. USA. 96:12079–12084. 10.1073/pnas.96.21.12079 [DOI] [PMC free article] [PubMed] [Google Scholar]

25. Kido Y., Tamai I., Okamoto M., Suzuki F., and Tsuji A.. 2000. Functional clarification of MCT1-mediated transport of monocarboxylic acids at the blood-brain barrier using in vitro cultured cells and in vivo BUI studies. Pharm. Res. 17:55–62. 10.1023/A:1007518525161 [DOI] [PubMed] [Google Scholar]

26. Bevilacqua M.P. 1993. Endothelial-leukocyte adhesion molecules. Annu. Rev. Immunol. 11:767–804. 10.1146/annurev.iy.11.040193.004003 [DOI] [PubMed] [Google Scholar]

27. Daneman R., Zhou L., Agalliu D., Cahoy J.D., Kaushal A., and Barres B.A.. 2010a The mouse blood-brain barrier transcriptome: a new resource for understanding the development and function of brain endothelial cells. PLoS One. 5:e13741 10.1371/journal.pone.0013741 [DOI] [PMC free article] [PubMed

28. Villemagne VL, Burnham S, Bourgeat P, *et al*. Amyloid ß deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. Lancet Neurol. 2013;12(4):357-367. [DOI] [PubMed] [Google Scholar]

29. Reiman EM, Quiroz YT, Fleisher AS, *et al*. Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: A case-control study. Lancet Neurol. 2012;11(2):1048-1056. [DOI] [PMC free article] [PubMed] [Google Scholar]

30. Jack CR, Lowe VJ, Weigand SD, *et al*. Serial PiB and MRI in normal, mild cognitive impairment and Alzheimer's disease: Implications for sequence of pathological events in Alzheimer's disease. Brain. 2009;132:1355-1365. [DOI] [PMC free article] [PubMed] [Google Scholar]

31. Bateman RJ, Xiong C, Benzinger TL, *et al*. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. N Engl J Med. 2012;367(9):795-804. [DOI] [PMC free article] [PubMed] [Google Scholar]

32. Gordon BA, Blazey TM, Su Y, *et al*. Spatial patterns of neuroimaging biomarker change in individuals from families with autosomal dominant Alzheimer's disease: A longitudinal study. Lancet Neurol. 2018;17(3):241-250. [DOI] [PMC free article] [PubMed] [Google Scholar]

33. Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST. Alzheimer disease and mortality: A 15-year epidemiological study. Arch Neurol. 2005;62(5):779-784. [DOI] [PubMed] [Google Scholar]

34. Waring SC, Doody RS, Pavlik VN, Massman PJ, Chan W. Survival among patients with dementia from a large multi-ethnic population. Alzheimer Dis Assoc Disord. 2005;19(4):178-183. [DOI] [PubMed] [Google Scholar]

35. Brookmeyer R, Corrada MM, Curriero FC, Kawas C. Survival following a diagnosis of Alzheimer disease. Arch Neurol. 2002; 59(11): 1764-1767. [DOI] [PubMed] [Google Scholar]

36. Dorahy G, Chen JZ, Balle T. Computer-Aided Drug Design towards New Psychotropic and Neurological Drugs. Molecules. 2023 Jan 30; 28(3): 1324. doi: 10.3390/molecules28031324. PMID: 36770990; PMCID: PMC9921936. https://pubmed.ncbi.nlm.nih.gov/36770990/

37. Penrose, R (1989). The Emperor's New Mind: Concerning Computers, Minds and the Laws of Physics, Oxford University Press, New York. [Google Scholar]

38. Hameroff, S, and Penrose, R (1996). "Orchestrated reduction of quantum coherence in brain microtubules: a model for consciousness." Math. Comput. Simul. 40, 453–480. 10.1016/0378-4754(96)80476-9 [DOI] [Google Scholar]

39. Tegmark, M (2000). "The importance of quantum decoherence in brain processes." Phys. Rev. E 61, 4194–4206. 10.1103/PhysRevE.61.4194 [DOI] [PubMed] [Google Scholar]

40. Eisert, J, and Wiseman, H, (2007). "Quantum aspects of life," In Nontrivial Quantum Effects in Biology: A Skeptical Physicists' View, World Scientific, Singapore. [Google Scholar]

41. McFadden, J (2000). Quantum Evolution: How Physics' Weirdest Theory Explains Life's Biggest Mystery, Harper Collins, New York. [Google Scholar]

42. Hornberger, K, Uttenthaler, S, Brezger, B, Hackermüller, L, Arndt, M, and Zeilinger, A (2003). "Collisional decoherence observed in matter wave Interferometry." Phys. Rev. Lett. 90, 160401. 10.1103/PhysRevLett.90.160401 [DOI] [PubMed] [Google Scholar]

43. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017 Mar 3;7:42717. doi: 10.1038/srep42717. PMID: 28256516; PMCID: PMC5335600. https://pubmed.ncbi.nlm.nih.gov/28256516/

44. Pires DE, Blundell TL, Ascher DB. pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. J Med Chem. 2015 May 14;58(9):4066-72. doi: 10.1021/acs.jmedchem.5b00104. Epub 2015 Apr 22. PMID: 25860834; PMCID: PMC4434528. https://pmc.ncbi.nlm.nih.gov/articles/PMC4434528/

45. Dulsat, J., López-Nieto, B., Estrada-Tejedor, R., & Borrell, J. I. (2023). Evaluation of Free Online ADMET Tools for Academic or Small Biotech Environments. Molecules, 28(2), 776. https://doi.org/10.3390/molecules28020776

46. Adriana Maria Viana Nunes, Francisco das Chagas Pereira de Andrade, Lívia Alves Filgueiras, Octávio Augusto de Carvalho Maia, Rodrigo L.O.R. Cunha, Sindy V.A. Rodezno, Antônio Luiz Martins Maia Filho, Fernando Aécio de Amorim Carvalho, Debora Cavalcante Braz, Anderson Nogueira Mendes,preADMET analysis and clinical aspects of dogs treated with the Organotellurium compound RF07: A possible control for canine visceral leishmaniasis?,Environmental Toxicology and Pharmacology,Volume 80,2020,103470,ISSN 1382-6689,https://doi.org/10.1016/j.etap.2020.103470.

47. Shaikh F, Siu SW. Identification of novel natural compound inhibitors for human complement component 5a receptor by homology modeling and virtual screening. Med Chem Res. 2016;25:1564-1573. doi: 10.1007/s00044-016-1591-1. Epub 2016 May 5. PMID: 27499603; PMCID: PMC4958400. https://pmc.ncbi.nlm.nih.gov/articles/PMC4958400/

48. Kuentz M, Nick S, Parrott N, Röthlisberger D. A strategy for preclinical formulation development using GastroPlus as pharmacokinetic simulation tool and a statistical screening design applied to a dog study. Eur J Pharm Sci. 2006 Jan;27(1):91-9. doi: 10.1016/j.ejps.2005.08.011. Epub 2005 Oct 10. PMID: 16219449. https://pubmed.ncbi.nlm.nih.gov/16219449/

49. Daina A, Zoete V. A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. ChemMedChem. 2016 Jun 6;11(11):1117-21. doi: 10.1002/cmdc.201600182. Epub 2016 May 24. PMID: 27218427; PMCID: PMC5089604. https://pubmed.ncbi.nlm.nih.gov/27218427/

50. Davit Gogolashvili, Bogdan Kozyrskiy, Maurizio Filippone,Locally Smoothed Gaussian Process Regression,Procedia Computer Science,Volume 207,2022,Pages 2717-2726,ISSN 1877-0509,https://doi.org/10.1016/j.procs.2022.09.330.

51. Epifanovsky E, Gilbert ATB, Feng X, Lee J, Mao Y, Mardirossian N, Pokhilko P,. Software for the frontiers of quantum chemistry: An overview of developments in the Q-Chem 5 package. J Chem Phys. 2021 Aug 28;155(8):084801. doi: 10.1063/5.0055522. PMID: 34470363; PMCID: PMC9984241. https://pmc.ncbi.nlm.nih.gov/articles/PMC9984241/

52. Neese F, Wennmohs F, Becker U, Riplinger C. The ORCA quantum chemistry program package. J Chem Phys. 2020 Jun 14;152(22):224108. doi: 10.1063/5.0004608. PMID: 32534543. https://pubmed.ncbi.nlm.nih.gov/32534543/

53. Tatiana Y. Zakharian, Shoshanna R. Coon,Evaluation of Spartan semi-empirical molecular modeling software for calculations of molecules on surfaces: CO adsorption on Ni(111),Computers & Chemistry,Volume 25, Issue 2,2001,Pages 135-144,ISSN 0097-8485. https://doi.org/10.1016/S0097-8485(00)00075-9.

54. Hassan H. Almasoudi, Mohammed H. Nahari, Targeting Plasmodium falciparum Schizont Egress Antigen-1 in Infected Red Blood Cells: Docking-Based Fingerprinting, Density Functional Theory, Molecular Dynamics Simulations, and Binding Free Energy Analysis, Pharmaceuticals, 10.3390/ph18020237, **18**, 2, (237), (2025). https://onlinelibrary.wiley.com/doi/full/10.1002/qua.24481