SIMULASI DINAMIKA MOLEKULER ANDROGRAFOLID DAN 2 TURUNANNYA TERHADAP *ACETYLCHOLINESTERASE* DAN *BETA-SECRETASE* 1 SEBAGAI KANDIDAT ANTI ALZHEIMER

SKRIPSI

ALMIRA PINKAN CARISSA
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SEKOLAH TINGGI FARMASI INDONESIA
YAYASAN HAZANAH
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Sebagai salah satu syarat untuk memperoleh gelar Sarjana Farmasi

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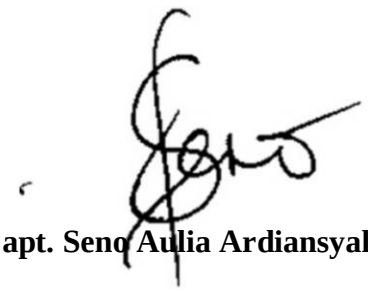
Juli 2026

Disetujui oleh :

Pembimbing	**Pembimbing**
	
apt. Seno Aulia Ardiansyah, M.Si	**apt. Maria Ulfah, M.Si**

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ABSTRAK

Penyakit Alzheimer merupakan penyakit neurodegeneratif progresif yang ditandai oleh penurunan fungsi kognitif dan memori, dengan *acetylcholinesterase* (AChE) dan β-*secretase* 1 (BACE1) sebagai dua target terapeutik utama. Penelitian ini bertujuan mengevaluasi potensi andrografolid, asam andrografik, dan 14-deoksi-11,12-didehidroandrografolid sebagai kandidat inhibitor multitarget AChE dan BACE1 melalui simulasi dinamika molekuler selama 10 ns, dengan donepezil dan verubecestat sebagai kontrol positif serta E20 dan M7D sebagai ligan alami. Parameter yang dianalisis meliputi *Root Mean Square Deviation*, *Root Mean Square Fluctuation*, okupansi ikatan hidrogen, dan energi bebas ikatan dengan metode MM-GBSA. Hasil simulasi menunjukkan bahwa seluruh kompleks uji mampu mempertahankan kestabilan konformasi, dengan 14-deoksi-11,12-didehidroandrografolid menunjukkan profil RMSD ligan paling stabil terhadap kedua reseptor, sementara fluktuasi residu terutama terjadi pada daerah loop dan terminal yang secara alami bersifat fleksibel. Analisis ikatan hidrogen menunjukkan interaksi persisten dengan residu-residu kunci pada sisi aktif kedua enzim. Berdasarkan perhitungan MM-GBSA, 14-deoksi-11,12-didehidroandrografolid menunjukkan afinitas pengikatan paling kompetitif terhadap AChE dengan nilai energi bebas total sebesar -42,9 kkal/mol, sedangkan andrografolid menunjukkan afinitas terbaik terhadap BACE1 dengan nilai -34,7 kkal/mol, mendekati ligan alami M7D. Secara keseluruhan, andrografolid dan turunannya berpotensi dikembangkan sebagai kandidat inhibitor multitarget AChE dan BACE1 untuk pengembangan agen terapeutik Alzheimer, meskipun validasi in vitro dan in vivo tetap diperlukan.

Kata kunci: Alzheimer, andrografolid, AChE, BACE1, *molecular docking*, dinamika molekuler, MM-GBSA.

ABSTRACT

Alzheimer's disease is a progressive neurodegenerative disease characterized by a decline in cognitive and memory functions, with acetylcholinesterase (AChE) and β-secretase 1 (BACE1) as two major therapeutic targets. This study aimed to evaluate the potential of andrographolide, andrographic acid, and 14-deoxy-11,12-didehydroandrographolide as multitarget inhibitors of AChE and BACE1 through 10 ns molecular dynamics simulations, with donepezil and verubecestat as positive controls and E20 and M7D as native ligands. The analyzed parameters included root mean square deviation, root mean square fluctuation, hydrogen bond occupancy, and binding free energy calculated using the MM-GBSA method. The simulation results showed that all test complexes were able to maintain conformational stability, with 14-deoxy-11,12-didehydroandrographolide exhibiting the most stable ligand RMSD profile toward both receptors, while residue fluctuations mainly occurred in loop and terminal regions that are naturally flexible. Hydrogen bond analysis revealed persistent interactions with key residues in the active sites of both enzymes. Based on the MM-GBSA calculations, 14-deoxy-11,12-didehydroandrographolide showed the most competitive binding affinity toward AChE, with a total free energy value of −42.9 kcal/mol, whereas andrographolide showed the best affinity toward BACE1, with a value of −34.7 kcal/mol, approaching that of the native ligand M7D. Overall, andrographolide and its derivatives have the potential to be developed as multitarget inhibitors of AChE and BACE1 for the development of therapeutic agents for Alzheimer's disease, although in vitro and in vivo validation is still required.

Keywords: *Alzheimer's disease, andrographolide, AChE, BACE1, molecular docking, molecular dynamics, MM-GBSA.*

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Bandung, Juli 2026

Penulis

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DAFTAR PUSTAKA

Adebambo, K., & Ojoh, O. (Claudia). (2024). In Silico Investigation of Novel Compounds as Inhibitors of Acetylcholinesterase Enzyme for the Treatment of Alzheimer's Diseases. *International Journal of Alzheimer's Disease*, *2024*, 1–19.

Al-Karmalawy, A. A., Dahab, M. A., Metwaly, A. M., Elhady, S. S., Elkaeed, E. B., Eissa, I. H., & Darwish, K. M. (2021). Molecular Docking and Dynamics Simulation Revealed the Potential Inhibitory Activity of ACEIs Against SARS-CoV-2 Targeting the hACE2 Receptor. *Frontiers in Chemistry*, *9*, 661230.

Alzheimer's Indonesia. (2019). Statistik Tentang Demensia - Alzheimer Indonesia. Diakses 11 Februari 2026.

Bao, L.-Q., Baecker, D., Mai Dung, D. T., Phuong Nhung, N., Thi Thuan, N., Nguyen, P. L., Phuong Dung, P. T., Huong, T. T. L., Rasulev, B., Casanola-Martin, G. M., Nam, N.-H., & Pham-The, H. (2023). Development of Activity Rules and Chemical Fragment Design for In Silico Discovery of AChE and BACE1 Dual Inhibitors against Alzheimer's Disease. *Molecules*, *28*(8), 3588.

Baroroh, U., Dasilva, J. A., Sundalian, M., Astriany, D., Ansori, A. N. M., & Yee, J. C. (2025). Exploring Brazilin as a Potential Breast Cancer Therapy via Molecular Dynamics Simulation Targeting ERα, 17β-HSD1, and NUDT5 Receptors. *Jurnal Kimia Valensi*, 11 (2), 226–237.

Baroroh, U., Yusuf, M., Rachman, S. D., Ishmayana, S., Hasan, K., & Subroto, T. (2019). Molecular Dynamics Study to Improve The Substrate Adsorption of Saccharomycopsis fibuligera R64 Alpha-amylase by Designing a New Surface Binding Site. *Advances and Applications in Bioinformatics and Chemistry*.

Bosco, F., Ruga, S., Citraro, R., Leo, A., Guarnieri, L., Maiuolo, J., Oppedisano, F., Macrì, R., Scarano, F., Nucera, S., Bava, I., Palma, E., Muscoli, C., Hancke, J., De Sarro, G., & Mollace, V. (2023). The Effects of Andrographis paniculata (Burm.F.) Wall. Ex Nees and Andrographolide on Neuroinflammation in the Treatment of Neurodegenerative Diseases. *Nutrients*, *15*(15), 3428.

Breijyeh, Z., & Karaman, R. (2020). Comprehensive Review on Alzheimer's Disease: Causes and Treatment. *Molecules*, *25*(24), 5789.

Case, D. A., Aktulga, H. M., Belfon, K., Ben-Shalom, I. Y., Brozell, S. R., Cerutti, D. S., Cheatham, T. E., Cruzeiro, V. W. D., Darden, T. A., Duke, R. E., Giambasu, G., Gilson, M. K., Gohlke, H., Goetz, A. W., Harris, R., Izadi, S., Izmailov, S. A., Jin, C., Kasavajhala, K., … Kollman, P. A. (2021). *Amber 2021*.

Case, D. A., Aktulga, H. M., Belfon, K., Cerutti, D. S., Cisneros, G. A., Cruzeiro, V. W. D., Forouzesh, N., Giese, T. J., Götz, A. W., Gohlke, H., Izadi, S.,

Kasavajhala, K., Kaymak, M. C., King, E., Kurtzman, T., Lee, T.-S., Li, P., Liu, J., Luchko, T., … Jr, K. M. M. (2023). AmberTools. *Journal of Chemical Information and Modeling*, *63*.

Cervellati, C., Valacchi, G., & Zuliani, G. (2021). BACE1: From biomarker to Alzheimer's Disease Therapeutical Target. *Aging*, *13*(9), 12299–12300.

Chakraborty, D., Berland, K., & Thonhauser, T. (2020). Next-Generation Nonlocal van der Waals Density Functional. *Journal of Chemical Theory and Computation*, *16*(9), 5893–5911.

Chauhan, E. S., Sharma, K., & Bist, R. (2019). *Andrographis paniculata*: A Review of its Phytochemistry and Pharmacological Activities. *Research Journal of Pharmacy and Technology*, *12*(2), 891.

Chen, C. T., Chang, C.-C., Chang, W.-N., Tsai, N.-W., Huang, C.-C., Chang, Y.-T., Wang, H.-C., Kung, C.-T., Su, Y.-J., Lin, W.-C., Cheng, B.-C., Su, C.-M., Hsiao, S.-Y., Hsu, C.-W., & Lu, C.-H. (2017). Neuropsychiatric Symptoms in Alzheimer's Sisease: Associations With Caregiver Burden and Treatment Outcomes. *QJM: An International Journal of Medicine*, *110*(9), 565–570.

Chen, Z.-R., Huang, J.-B., Yang, S.-L., & Hong, F.-F. (2022). Role of Cholinergic Signaling in Alzheimer's Disease. Molecules, 27(6), 1816.

Chen, J., Zhang, S., Wang, W., Sun, H., Zhang, Q., & Liu, X. (2021). Binding of Inhibitors to BACE1 Affected by pH-Dependent Protonation: An Exploration from Multiple Replica Gaussian Accelerated Molecular Dynamics and MM-GBSA Calculations. *ACS Chemical Neuroscience*, *12*(14), 2591–2607.

Chidambaram, K. (2023). Identification of BACE-1 Inhibitors Against Alzheimer's Disease Through E-Pharmacophore-Based Virtual Screening and Molecular Dynamics Simulation Studies: An Insilco Approach. *Life*, *13*(4), 952.

Coimbra, J. R. M., Marques, D. F. F., Baptista, S. J., Pereira, C. M. F., Moreira, P. I., Dinis, T. C. P., Santos, A. E., & Salvador, J. A. R. (2018). Highlights in BACE1 Inhibitors for Alzheimer's Disease Treatment. *Frontiers in Chemistry*, *6*, Article 178.

D'Argenio, V., & Sarnataro, D. (2020). New insights into the molecular bases of familial Alzheimer's disease. *Journal of Personalized Medicine*, *10*(2), 26.

DeTure, M. A., & Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. *Molecular Neurodegeneration*, *14*(1), 32.

Dasmahapatra, U., Kumar, C. K., Das, S., Subramanian, P. T., Murali, P., Isaac, A. E., Ramanathan, K., Mm, B., & Chanda, K. (2022). In-silico Molecular Modelling, MM/GBSA Binding Free Energy and Molecular Dynamics Simulation Study of Novel Pyrido Fused Imidazo[4,5-c]quinolines as potential anti-tumor agents. *Frontiers in Chemistry*, *10*, 991369.

Dermawan, D., & Alotaiq, N. (2025). Rescuing Verubecestat: An Integrative Molecular Modeling and Simulation Approach for Designing Next-Generation BACE1 Inhibitors. *International Journal of Molecular Sciences*, *26*(24), 12143.

Fatriansyah, J. F., Boanerges, A. G., Kurnianto, S. R., Pradana, A. F., Fadilah, & Surip, S. N. (2022). Molecular Dynamics Simulation of Ligands from Anredera cordifolia (Binahong) to the Main Protease (Mpro) of SARS-CoV-2. *Journal of Tropical Medicine*, *2022*, 1–13.

Forouzesh, N., & Mishra, N. (2021). An Effective MM/GBSA Protocol for Absolute Binding Free Energy Calculations: A Case Study on SARS-CoV-2 Spike Protein and the Human ACE2 Receptor. *Molecules*, *26*(8), 2383.

Fu, Y., Zhao, J., & Chen, Z. (2018). Insights into the Molecular Mechanisms of Protein-Ligand Interactions by Molecular Docking and Molecular Dynamics Simulation: A Case of Oligopeptide Binding Protein. *Computational and Mathematical Methods in Medicine*, *2018*, 1–12.

Ghosh, A. K. (2024). BACE1 Inhibitor Drugs For the Treatment of Alzheimer's disease: Lessons Learned, Challenges to Overcome, and Future Prospects . *Global Health & Medicine*, *6*(3), 164–169.

Gu, L., Lu, J., Li, Q., Wu, N., Zhang, L., Li, H., Xing, W., & Zhang, X. (2020). A Network-based Analysis of Key Pharmacological Pathways of Andrographis Paniculata Acting on Alzheimer's Disease And Experimental Validation. *Journal of Ethnopharmacology*, *251*, 112488.

Hampel, H., Mesulam, M.-M., Cuello, A. C., Farlow, M. R., Giacobini, E., Grossberg, G. T., Khachaturian, A. S., Vergallo, A., Cavedo, E., Snyder, P. J., & Khachaturian, Z. S. (2018). The Cholinergic System in The Pathophysiology And Treatment of Alzheimer's Disease. *Brain*, 141(7), 1917–1933.

Hampel, H., Mesulam, M.-M., Cuello, A. C., Khachaturian, A. S., Vergallo, A., Farlow, M. R., Snyder, P. J., Giacobini, E., & Khachaturian, Z. S. (2019). Revisiting the Cholinergic Hypothesis in Alzheimer's Disease: Emerging Evidence from Translational and Clinical Research. *The Journal of Prevention of Alzheimer's Disease*, 6(1), 2–15.

Hollingsworth, S. A., & Dror, R. O. (2018). Molecular Dynamics Simulation for All Neuron, 99(6), 1129–1143.

Hu, M., Zheng, M., Wang, C., Li, Q., Li, J., Zhou, X., Ying, X., Quan, S., Gu, L., & Zhang, X. (2024). Andrographolide Derivative Andro-III Modulates Neuroinflammation And Attenuates Neuropathological Changes of Alzheimer's Disease Via GSK-3β/NF-κB/CREB Pathway. *European Journal of Pharmacology*, *965*, 176305.

J. R. Yunta, M. (2017). It Is Important to Compute Intramolecular Hydrogen Bonding in Drug Design? *American Journal of Modeling and Optimization*, *5*(1), 24–57.

Ischak, N. I., & Botutihe, D. N. (2018). *Sambiloto, Ceplukan, Daun Salam (Antidiabetes)*. Universitas Negeri Gorontalo Press.

Jacobsen, A., van Dijk, E., Mouhib, H., Stringer, B., Ivanova, O., Gavaldá-Garciá, J., Hoekstra, L., Feenstra, K. A., & Abeln, S. (2023). *Introduction to Protein Structure* (Version 2). arXiv.

Joseph, S., & Joseph, J. (2016). Bicyclic Diterpenoid and Phytosterol Constituents from Andrographis Paniculata (Nees). *Oriental Journal of Chemistry*, *32*(4), 2231–2233.

Karlina, I., Andriyani, E. F. S., Pratiwi, A. D., Prasasti, F. F. T. A., Tunjung, W. A. S., Rohmah, Z., & Nuriliani, A. (2024). Gambaran Penyakit Neurodegeneratif: Huntington, Alzheimer, dan Parkinson: Sebuah Tinjauan. *Jurnal Biomedika Dan Kesehatan*, *7*(1), 113–123.

Kaur, R. (2025). Inhibition Mechanism of Amidine based Oxazine Derivative Against BACE1 Activity. *Machine Learning*, Volume 26 : 2.

Knopman, D. S., Amieva, H., Petersen, R. C., Chételat, G., Holtzman, D. M., Hyman, B. T., Nixon, R. A., & Jones, D. T. (2021). Alzheimer Disease. *Nature Reviews Disease Primers*, *7*(1), 33.

Komari, N., Hadi, S., & Suhartono, E. (2020). Pemodelan Protein dengan Homology Modeling menggunakan SWISS-MODEL: Protein Modeling with Homology Modeling using SWISS-MODEL. *Jurnal Jejaring Matematika dan Sains*, *2*(2), 65–70.

Kurban, M. G., & Şentürk, M. (2024). Kolinesteraz İnhibitörlerinin Alzheimer Hastalığı Tedavisindeki Rolü. *Ağrı Tıp Fakültesi Dergisi*, *2*(1), 42–45.

Lemkul, J. A. (2018). From Proteins to Perturbed Hamiltonians: A Suite of Tutorials for the GROMACS-2018 Molecular Simulation Package [Article v1.0]. *Living Journal of Computational Molecular Science*, *1*(1), 5068.

McShane, R., Westby, M. J., Roberts, E., Minakaran, N., Schneider, L., Farrimond, L. E., Maayan, N., Ware, J., & Debarros, J. (2019). Memantine For Dementia. *Cochrane Database of Systematic Reviews*.

Mintun, M. A., Lo, A. C., Duggan Evans, C., Wessels, A. M., Ardayfio, P. A., Andersen, S. W., Shcherbinin, S., Sparks, J., Sims, J. R., Brys, M., Apostolova, L. G., Salloway, S. P., & Skovronsky, D. M. (2021). Donanemab in Early Alzheimer's Disease. *New England Journal of Medicine,* 384(18), 1691–1704.

Plascencia-Villa, G., & Perry, G. (2022). Neuropathologic Changes Provide Insights into Key Mechanisms of Alzheimer Disease and Related Dementia. *The American Journal of Pathology*, *192*(10), 1340–1346.

Putri, N. P. A. (2024). Efek Terapeutik Andrografolid terhadap Penyakit Alzheimer: Tinjauan Sifat Antiinflamasi, Antioksidan, dan Neuroprotektif. *Prosiding Workshop Dan Seminar Nasional Farmasi 2024*, *3*.

Putri, T. Z. A. D., Findrayani, R. P., Isrul, M., & Lolok, N. (2024). Studi Molecular Docking Senyawa Kimia Dari Herba Putri Malu (Mimosa pudica) Terhadap Inhibisi Enzim A-Glukosidase Sebagai Antidiabetes Melitus. *Jurnal Pharmacia Mandala Waluya*, *3*(4), 225–233.

Safiri, S., Ghaffari Jolfayi, A., Fazlollahi, A., Morsali, S., Sarkesh, A., Daei Sorkhabi, A., Golabi, B., Aletaha, R., Motlagh Asghari, K., Hamidi, S., Mousavi, S. E., Jamalkhani, S., Karamzad, N., Shamekh, A., Mohammadinasab, R., Sullman, M. J. M., Şahin, F., & Kolahi, A.-A. (2024). Alzheimer's Disease: A Comprehensive Review of Epidemiology, Risk Factors, Symptoms Diagnosis, Management, Caregiving, Advanced Treatments And Associated Challenges. *Frontiers in Medicine*, *11*, 1474043.

Salo-Ahen, O. M. H., Alanko, I., Bhadane, R., Bonvin, A. M. J. J., Honorato, R. V., Hossain, S., Juffer, A. H., Kabedev, A., Lahtela-Kakkonen, M., Larsen, A. S., Lescrinier, E., Marimuthu, P., Mirza, M. U., Mustafa, G., Nunes-Alves, A., Pantsar, T., Saadabadi, A., Singaravelu, K., & Vanmeert, M. (2020). Molecular Dynamics Simulations in Drug Discovery and Pharmaceutical Development. *Processes*, *9*(1), 71.

Saudale, F. Z. (2020). Pemodelan Homologi Komparatif Struktur 3d Protein dalam Desain dan Pengembangan Obat. *Al-Kimia*, *8*(1).

Shukla, A. K., Yadav, V. K., Maurya, R. K., Mishra, R., Srivastava, S., & Mishra, M. K. (2025). Andrographolide-A Magical Bioactive Compound: An Overview. *Current Traditional Medicine*, *11*(4), e270224227462.

Singh, A., & Jha, A. (2021). Cholinesterase Inhibitors Used for the Management of Alzheimer's Disease: A Review. *Journal of Pharmaceutical Research International*, 121–128.

Singh, A. K., Rai, S. N., Maurya, A., Mishra, G., Awasthi, R., Shakya, A., Chellappan, D. K., Dua, K., Vamanu, E., Chaudhary, S. K., & Singh, M. P. (2021). Therapeutic Potential of Phytoconstituents in Management of Alzheimer's Disease. *Evidence-Based Complementary and Alternative Medicine*, *2021*, 1–19.

Singh, A., & Mishra, A. (2021). Leucoefdin a potential inhibitor against SARS CoV-2 M^{pro}. *Journal of Biomolecular Structure and Dynamics*, *39*(12), 4427–4432.

Suhartono, E., Budianto, W. Y., Sekartaji, H. L., Fahira, N. S., & Cahyadi, H. (2018). Hubugan Kadar Enzim Asetilkolinesterase Terhadap Kadar Glukosa Petani yang Terpajan Pestisida (Pt 2). *Jurnal Publikasi Kesehatan Masyarakat Indonesia*, *5*.

Tiemann, J. K., Szczuka, M., Bouarroudj, L., Oussaren, M., Garcia, S., Howard, R. J., Delemotte, L., Lindahl, E., Baaden, M., Lindorff-Larsen, K., Chavent, M., & Poulain, P. (2024). MDverse, Shedding Light on The Dark Matter of Molecular Dynamics Simulations. *eLife*, *12*, RP90061.

Trezza, A., Visibelli, A., Roncaglia, B., Barletta, R., Iannielli, S., Mahboob, L., Spiga, O., & Santucci, A. (2025). Unveiling Dynamic Hotspots in Protein–Ligand Binding: Accelerating Target and Drug Discovery Approaches. *International Journal of Molecular Sciences*, *26*(9), 3971.

Tsalitsah, S. A. R. (2025). Studi In Silico Aktivitas Penghambat Acetylcholinesterase Dan Beta-secretase Senyawa Andrografolid Serta Turunannya Sebagai Anti Alzheimer.

Turana, Y., Tengkawan, J., Suswanti, I., Suharya, D., Riyadina, W., & Pradono, J. (2019). Primary Prevention of Alzheimer's Disease in Indonesia. *International Journal of Aging Research*.

Tuzimski, T., & Petruczynik, A. (2022). Determination of Anti-Alzheimer's Disease Activity of Selected Plant Ingredients. Molecules, 27(10), 3222.

Twana Salih. (2022). Evaluating the Reliability of MM-PB/GB-SA Method for the Protein-Ligand Binding Free Energies Using Penicillopepsin-Inhibitor ligands. *Al Mustansiriyah Journal of Pharmaceutical Sciences*, *22*(3), 51–64.

Van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., Cohen, S., Froelich, L., Katayama, S., Sabbagh, M., Vellas, B., Watson, D., Dhadda, S., Irizarry, M., Kramer, L. D., & Iwatsubo, T. (2023). Lecanemab in Early Alzheimer's Disease. *New England Journal of Medicine*, 388(1), 9–21.

van Oostveen, W. M., & de Lange, E. C. M. (2021). Imaging techniques in Alzheimer's disease: A review of applications in early diagnosis and longitudinal monitoring. *International Journal of Molecular Sciences, 22*(4), 2110.

Wang, Y., Yang, F., Yan, D., Zeng, Y., Wei, B., Chen, J., & He, W. (2023). Identification Mechanism of BACE1 on Inhibitors Probed by Using Multiple Separate Molecular Dynamics Simulations and Comparative Calculations of Binding Free Energies. *Molecules, 28*(12), 4773.

Waterhouse, A., Bertoni, M., Bienert, S., Studer, G., Tauriello, G., Gumienny, R., Heer, F. T., de Beer, T. A. P., Rempfer, C., Bordoli, L., Lepore, R., & Schwede, T. (2018). SWISS-MODEL: Homology modelling of protein structures and complexes. *Nucleic Acids Research, 46*(W1), W296–W303.

Xiao, H., Gui, Y., Li, X., Dai, W., Feng, C., Li, G., & Luo, J. (2024). Explore on Screening COX-2 inhibitors From The Essential Oil of Solanum Lyratum Thunb. By Molecular Docking And Molecular Dynamics Simulation. *Heliyon, 10*(18), e37652.

Yiannopoulou, K. G., & Papageorgiou, S. G. (2020). Current and Future Treatments in Alzheimer Disease: An Update. *Journal of Central Nervous System Disease, 12*, 117957352090739.

Yunita, E. (2021). Mekanisme Kerja Andrografolid Dari Sambiloto Sebagai Senyawa Antioksidan. *Herb-Medicine Journal*, *4*(1), 43.

Zhang, J., Zhang, Y., Wang, J., Xia, Y., Zhang, J., & Chen, L. (2024). Recent advances in Alzheimer's disease: Mechanisms, clinical trials and new drug development strategies. *Signal Transduction and Targeted Therapy, 9*(1), Article 211.

Zikri, A. T., Pranowo, H. D., & Haryadi, W. (2020). Stability, Hydrogen Bond Occupancy Analysis and Binding Free Energy Calculation from Flavonol Docked in DAPK1 Active Site Using Molecular Dynamic Simulation Approaches. *Indonesian Journal of Chemistry*, *21*(2), 383.