PENAMBATAN MOLEKULER FULVESTRANT PADA RESEPTOR ESTROGEN DAN VARIAN POLIMORFISMENYA SECARA *IN SILICO*

SKRIPSI

diajukan sebagai salah satu syarat untuk memperoleh gelar Sarjana Sains
Program Studi Biologi

oleh
Dwi Fitriawati Fajrin
1900480

PROGRAM STUDI BIOLOGI
FAKULTAS PENDIDIKAN MATEMATIKA DAN ILMU PENGETAHUAN ALAM
UNIVERSITAS PENDIDIKAN INDONESIA
BANDUNG
2023

PENAMBATAN MOLEKULER FULVESTRANT PADA RESEPTOR ESTROGEN DAN VARIAN POLIMORFISMENYA SECARA *IN SILICO*

Oleh

Dwi Fitriawati Fajrin

Sebuah skripsi yang diajukan untuk memenuhi salah satu syarat memperoleh gelar Sarjana Sains pada Program Studi Biologi,
Fakultas Pendidikan Matematika dan Ilmu Pengetahuan Alam

Universitas Pendidikan Indonesia 2023
November 2023

LEMBAR PENGESAHAN

(Dwi Fitriawati Fajrin)

PENAMBATAN MOLEKULER FULVESTRANT PADA RESEPTOR ESTROGEN DAN VARIAN POLIMORFISMENYA SECARA *IN SILICO*

Disetujui dan disahkan oleh:

Pembimbing I

Dr. Hj. Diah Kusumawaty, M.Si.

NIP: 197008112001122001

Pembimbing II

Dr. Any Aryani, M.Si.

NIP. 197105302001122001

Pembimbing III

Prof. Dr. Trina Ekawati Tallei, M.Si.

NIP. 196605081995122001

Mengetahui,

Ketua Program Studi Biologi

Dr. H. Wahyu Surakusumah, M.T

NIP 197212301999031001

LEMBAR PERNYATAAN

Dengan ini saya menyatakan bahwa skripsi dengan judul "Penambatan Molekuler Fulvestrant pada Reseptor Estrogen dan Varian Polimorfismenya secara *In Silico*" ini beserta seluruh isinya adalah benar-benar karya saya sendiri. Saya tidak melakukan penjiplakan atau pengutipan dengan cara-cara yang tidak sesuai dengan etika ilmu yang berlaku dalam masyarakat keilmuan. Atas pernyataan ini, saya siap menanggung sanksi apabila di kemudian hari ditemukan adanya pelanggaran etika keilmuan atau ada klaim dari pihak lain terhadap keaslian karya saya ini.

Bandung, November 2023

Yang membuat pernyataan

Dwi Fitriawati Fajrin

NIM. 1900480

ABSTRAK

Penambatan Molekuler Fulvestrant pada Reseptor Estrogen dan Varian Polimorfismenya secara *In Silico*

Salah satu penyakit paling banyak menyebabkan kematian didunia adalah penyakit kanker. Kanker payudara adalah kasus paling banyak kanker yang diderita pada perempuan. ER atau *Estrogen Receptor* adalah reseptor yang berperan dalam perkembangan sel kanker payudara. Terdapat lebih dari 70% penderita kanker payudara memiliki status hormonal dengan kategori ER positif. ER alpha diketahui adalah target terapi dalam pengobatan kanker payudara ER positif. Diketahui pada ER alpha terdapat beberapa polimorfisme. Pada kasus polimorfisme ini diketahui dapat mempengaruhi fungsi protein salah satunya adalah resistensi terhadap terapi obat. Penelitian ini bertujuan untuk mengetahui interaksi Fulvestrant sebagai salah satu obat standar yang digunakan dalam pengobatan kanker payudara terhadap polimorfisme ER D538G, Y537S, Y537N, Y537C, dan L536R yang dilakukan secara *in silico*. Berdasarkan penelitian yang telah dilakukan menunjukkan bahwa Fulvestrant masih dapat direkomendasikan pada penderita kanker payudara dengan polimorfisme D538G, Y537S, Y537N, Y537C, dan L536R. Hasil temuan yang didapatkan diketahui polimorfisme pada asam amino 536, 537, dan 538 tidak memiliki peran yang signifikan dalam pengikatannya pada ligan. Hasil dari penelitian yang telah dilakukan ini dapat menjadi referensi pada penelitian yang akan datang terkait peran polimorfisme pada pengikatannya dengan ligan terutama pada reseptor ER.

Kata Kunci : Kanker Payudara, ER, Fulvestrant, Polimorfisme, Penambatan Molekuler

ABSTRACT

In Silico Approach for Molecular Docking of Fulvestrant with Estrogen Receptor and its Polymorphic Variants

One of the diseases that causes the most death in the world is cancer. The most frequent type of cancer among woman is breast cancer. ER or Estrogen Receptor is a receptor that has a role in the growth of breast cancer cells. More than 70% of breast cancer patient have the ER positive category hormonal status in. ER alpha is known to be a therapeutic target of the treatment in ER positive breast cancer. It is known that ER alpha contains several polymorphisms. In the case of this polymorphism, it is known that it can affect protein function, one of them is resistance to drug therapy. The aim of this research is to know the interaction of Fulvestrant as one the drugs that used in the breast cancer treatment with the ER polymorphisms D538G, Y537S, Y537N, Y537C, and L536R, by in silico method. Based on the research, it shows that Fulvestrant can still be recommended for breast cancer patient with the D538G, Y537S, Y537N, Y537C, and L536R polymorphisms. The findings obtained show that polymorphisms in amino acids 536, 537, and 538 do not have a significant role in binding to the ligand. The findings from this research can be used as a reference in future research regarding the role of polymorphism in binding to ligands, especially ER receptors.

Keywords: Breast Cancer, ER, Fulvestrant, Polymorphism, Molecular Docking

DAFTAR ISI

DAFTAR TABEL

DAFTAR GAMBAR

DAFTAR LAMPIRAN

DAFTAR PUSTAKA

Agus, N. A., Holik, H. A., & Achmad, A. (2022). Kemajuan Terkini dalam Radiofarmaka sebagai Agen Terapi Kanker Payudara. *Farmaka*, *20*(2), 121–135. http://jurnal.unpad.ac.id/farmaka/article/view/39356

American cancer society. (2022). *What is cancer?*. Diakses dari https://www.cancer.org/cancer/understanding-cancer/what-is-cancer.html

Al-Mubarak, M., Sacher, A. G., Ocana, A., Vera-Badillo, F., Seruga, B., & Amir, E. (2013). Fulvestrant for advanced breast cancer: A meta-analysis. In *Cancer Treatment Reviews*. https://doi.org/10.1016/j.ctrv.2013.03.004

Aliwikarta, K., Palupi, N. S., & Giriwono, P. E. (2016). Prevalensi Penyakit Kanker di Indonesia Berdasarkan Pola Konsumsi Pangan dan Gaya Hidup Cancer prevalence in Indonesia Based on Food Consumption Patterns and Lifestyle Newly Weds Foods Asia Pacific 2. *Jurnal Mutu Pangan*, *3*(1), 71–78.

Amelia, F. (2014). Studi Interaksi Ligan Peptidoid dan Peptida Dengan Enzim Protease NS3/NS2B Virus Dengue. *Jurnal Sainstek*, *6*(1), 24–29.

Ayaz, G., Yasar, P., Olgun, C. E., Karakaya, B., Kars, G., Razizadeh, N., Yavuz, K., Turan, G., & Muyan, M. (2019). Dynamic transcriptional events mediated by estrogen receptor alpha. *Frontiers in Bioscience - Landmark*, *24*(2), 245–276. https://doi.org/10.2741/4716

Baroroh, U., Muscifa, Z. S., Destiarani, W., Rohmatullah, F. G., & Yusuf, M. (2023). Molecular interaction analysis and visualization of protein-ligand docking using Biovia Discovery Studio Visualizer. *Indonesian Journal of Computational Biology (IJCB)*, *2*(1), 22. https://doi.org/10.24198/ijcb.v2i1.46322

Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N., & Bourne, P. E. (2000). The Protein Data Bank. *Nucleic Acids Research*, *28*(1), 235–242. https://doi.org/10.1038/s41577-020-00473-z

Boér, K. (2017). Fulvestrant in advanced breast cancer: evidence to date and place in therapy. *Therapeutic Advances in Vaccines*, *9*(7), 465–479. https://doi.org/10.1177/https

Bosco, K. H., & Brasseur, R. (2005). The Ramachandran plots of glycine and pre-proline. *BMC Structural Biology*, *5*(14), 1–11. https://doi.org/10.1186/1472-6807-5-14

Breast Cancer Now.(2018). *Fulvestrant (Faslodex)*. Diakses dari https://breastcancernow.org/information-support/facing-breast-cancer/going-through-treatment-breast-cancer/hormone-therapy/fulvestrant-faslodex

Bross, P. F., Baird, A., Chen, G., Jee, J. M., Lostritto, R. T., Morse, D. E., Rosario, L. A., Williams, G. M., Yang, P., Rahman, A., Williams, G., & Pazdur, R. (2003). Fulvestrant in postmenopausal women with advanced breast cancer. *Clinical Cancer Research*, *9*(12), 4309–4317.

Carugo, O., & Pongor, S. (2008). A normalized root-mean-spuare distance for comparing protein three-dimensional structures. *Protein Science*, *10*(7), 1470–1473. https://doi.org/10.1110/ps.690101

Chen, P., Li, B., & Ou-Yang, L. (2022). Role of estrogen receptors in health and disease. *Frontiers in Endocrinology*, *13*, 1–25. https://doi.org/10.3389/fendo.2022.839005

Chu, W. T., & Zheng, Q. C. (2013). Conformational changes of enzymes and DNA in molecular dynamics: Influenced by pH, temperature, and ligand. In *Advances in Protein Chemistry and Structural Biology* (1st ed., Vol. 92). Copyright © 2013 Elsevier Inc. All rights reserved. https://doi.org/10.1016/B978-0-12-411636-8.00005-5

Coimbra, J. T. S., Feghali, R., Ribeiro, R. P., Ramos, M. J., & Fernandes, P. A. (2020). The importance of intramolecular hydrogen bonds on the translocation of the small drug piracetam through a lipid bilayer. *RSC Advances*, *11*(2), 899–908. https://doi.org/10.1039/d0ra09995c

Cowley, S. M., Hoare, S., Mosselman, S., & Parker, M. G. (1997). Estrogen receptors α and β form heterodimers on DNA. *Journal of Biological Chemistry*, *272*(32), 19858–19862. https://doi.org/10.1074/jbc.272.32.19858

Creighton, T. E. (1990). Protein folding. *Biochem*, *270*, 1–16. https://doi.org/10.1007/978-981-10-4968-2_2

Csizmadia, P. (1999). MarvinSketch and MarvinView: Molecule Applets for the World Wide Web. *Third International Electronic Conference on Synthetic Organic Chemistry*. https://doi.org/10.3390/ecsoc-3-01775

Dang, D. T. (2022). Molecular Approaches to Protein Dimerization: Opportunities for Supramolecular Chemistry. *Frontiers in Chemistry*, *10*, 1–12. https://doi.org/10.3389/fchem.2022.829312

Daraz, F., Windarti, I., & Putu, R. A. S. (2023). Peran Obesitas dalam Metastasis Kanker Payudara. *Medula*, *13*(1), 172–178.

EBE. (2015). *White Paper on Personalized Medicine*. Diakses dari: http://www.ebe-biopharma.eu/uploads/EBE-biopharma_WhitePaperOnPM_RGB.pdf

Ekins, S., Mestres, J., & Testa, B. (2007). In silico pharmacology for drug discovery: Applications to targets and beyond. *British Journal of Pharmacology*, *152*(1), 21–37. https://doi.org/10.1038/sj.bjp.0707306

Elfita, L., Apriadi, A., Supandi, S., & Dianmurdedi, S. (2022). Studi Penambatan Molekuler dan Simulasi Dinamika Molekuler Senyawa Turunan Furanokumarin terhadap Reseptor Estrogen Alfa (ER-α) Sebagai Anti Kanker Payudara. *Jurnal Sains Farmasi & Klinis*, *9*(3), 255. https://doi.org/10.25077/jsfk.9.3.255-264.2022

Enmark, E., Pelto-Huikko, M., Grandien, K., Lagercrantz, S., Lagercrantz, J., Fried, G., Nordenskjöld, M., & Gustafsson, J. Å. (1997). Human estrogen receptor β-gene structure, chromosomal localization, and expression pattern. *Journal of Clinical Endocrinology and Metabolism*, *82*(12), 4258–4265. https://doi.org/10.1210/jcem.82.12.4470

Essoussi, N., Boujenfa, K., & Limam, M. (2008). A comparison of MSA tools. *Bioinformation*, *2*(9), 452–455. https://doi.org/10.6026/97320630002452

Faisal, H. K. P., Zaini, J., & Yunus, F. (2020). Next-Generation Sequencing pada Kanker Paru Next-Generation Sequencing in Lung Cancer. *E Jurnal Kedokteran Indonesia*, *8*(2). https://doi.org/10.23886/ejki.8.11579

Ferguson, J. R., Harding, J. R., Killick, D. A., Lumbard, K. W., Scheinmann, F., & Stachulski, A. V. (2001). Putative metabolites of fulvestrant, an estrogen receptor downregulator. Improved glucuronidation using trichloroacetimidates. *Journal of the Chemical Society. Perkin Transactions 1*, *22*, 3037–3041. https://doi.org/10.1039/b105397n

Fidianingsih, I. (2013). 6721-11667-1-SM.pdf. In *Personalized Medicine Untuk Penderita Kanker* (Vol. 5, Issue 2).

Fitri, D. E. W. (2023). *Penambatan Molekuler Pioglitazone Terhadap Varian Polimorfisme Reseptor PPARγ Pada Diabetes Melitus Tipe 2*. (Skripsi). Fakultas Matematika dan Ilmu Pengetahuan Alam, Universitas Sam Ratulangi, Manado.

Fuentes, N., & Silveyra, P. (2019). Estrogen receptor signaling mechanism. *Adv Protein Chem Struct Biol*, *116*, 135–170. https://doi.org/10.1016/bs.apcsb.2019.01.001.Estrogen

Gita, S. (2015). Peran Bioinformatika dalam Desain Kandidat Molekul Obat. *Biotrends*, *1*(1), 25–27. http://terbitan.biotek.lipi.go.id/index.php/biotrends/article/view/10%0Ahttps://www.researchgate.net/publication/317011679_Peran_Bioinformatika_dalam_Desain_Kandidat_Molekul_Obat

GLOBOCAN/GCO(Global Cancer Observatory).(2021). *Cancer Today*. Diakses dari https://gco.iarc.fr/

Green, S., Walter, P., Kumar, V., Krust, A., Bornert, J. M., Argos, P., & Chambon, P. (1986). Human oestrogen receptor cDNA: Sequence, expression and homology to v-erb-A. *Nature*, *320*(6058), 134–139. https://doi.org/10.1038/320134a0

Gutnik, D., Evseev, P., Miroshnikov, K., & Shneider, M. (2023). Using AlphaFold Predictions in Viral Research. *Current Issues in Molecular Biology*. *45*(4), 3705-3732. https://doi.org/10.3390/cimb45040240

Hakim, A., Widyanti, W., & Alfianto, U. (2018). HUBUNGAN ANTARA OBESITAS DENGAN RESEPTOR HORMONAL (Reseptor Estrogen dan Progesteron) DAN EKSPRESI HER-2/NEU PADA PASIEN KANKER PAYUDARA DI RS X SURAKARTA. *Biomedika*, *10*(1), 30–34. https://doi.org/10.23917/biomedika.v10i1.5851

Haldosén, L. A., Zhao, C., & Dahlman-Wright, K. (2014). Estrogen receptor beta in breast cancer. *Molecular and Cellular Endocrinology*, *382*(1), 665–672. https://doi.org/10.1016/j.mce.2013.08.005

Harbeck, N., Penault-Llorca, F., Cortes, J., Gnant, M., Houssami, N., Poortmans, P., Ruddy, K., Tsang, J., & Cardoso, F. (2019). Breast cancer. In *Nature Reviews Disease Primers* (Vol. 5, Issue 1). https://doi.org/10.1038/s41572-019-0111-2

Harrod, A., Lai, C. F., Goldsbrough, I., Simmons, G. M., Oppermans, N., Santos, D. B., Győrffy, B., Allsopp, R. C., Toghill, B. J., Balachandran, K., Lawson, M., Morrow, C. J., Surakala, M., Carnevalli, L. S., Zhang, P., Guttery, D. S., Shaw, J. A., Coombes, R. C., Buluwela, L., & Ali, S. (2022). Genome engineering for estrogen receptor mutations reveals differential responses to anti-estrogens and new prognostic gene signatures for breast cancer. *Oncogene*, *41*(44), 4905–4915. https://doi.org/10.1038/s41388-022-02483-8

Hendlich, M., Rippmann, F., & Barnickel, G. (1997). LIGSITE: Automatic and efficient detection of potential small molecule-binding sites in proteins. *Journal of Molecular Graphics and Modelling*, *15*(6), 359–363. https://doi.org/10.1016/S1093-3263(98)00002-3

Hernando, C., Ortega-Morillo, B., Tapia, M., Moragón, S., Martínez, M. T., Eroles, P., Garrido-Cano, I., Adam-Artigues, A., Lluch, A., Bermejo, B., & Cejalvo, J. M. (2021). Oral selective estrogen receptor degraders (Serds) as a novel breast cancer therapy: Present and future from a clinical perspective. *International Journal of Molecular Sciences*, *22*(15). https://doi.org/10.3390/ijms22157812

Hernndez-Santoyo, A., Yair, A., Altuzar, V., Vivanco-Cid, H., & Mendoza-Barrer, C. (2013). Protein-Protein and Protein-Ligand Docking. *Protein Engineering - Technology and Application*, *Figure 1*. https://doi.org/10.5772/56376

Hillisch, A., & Hilgenfeld, R. (2003). The role of protein 3D-structures in the drug discovery process. In *Modern Methods of Drug Discovery*. https://doi.org/10.1007/978-3-0348-7997-2_8

Huang, T.S., & Ang, P.(2018).[*Online*]. TERAPI HORMONAL DALAM KANKER PAYUDARA LANJUT DAN CARA BARU UNTUK MENGATASI RESISTENSI. Diakses dari https://oncocare.sg/id/blogs/terapi-hormonal-dalam-kanker-payudara-lanjut-dan-agen-baru-untuk-mengatasi-resisten/

Ibrahim, F., Huang, B., Xing, J. Z., Roa, W., & Gabos, S. (2009). Effects of Estrogen Contamination on Human Cells: Modeling and Prediction Based on Michaelis-Menten Kinetics. *Journal of Water Resource and Protection*, *01*(05), 336–344. https://doi.org/10.4236/jwarp.2009.15040

Jackson, A., & Powers, H. (2018). The Cancer Process. In *JAmerica Insitue for Cancer Research*. https://doi.org/10.1001/jama.1930.02720200064036

Jenuth, J. P. (2000). *The NCBI. Publicly available tools and resources on the Web.* Methods in Molecular Biology (Clifton, N.J.). https://doi.org/10.1385/1-59259-192-2:301

Jia, M., Dahlman-Wright, K., & Gustafsson, J. Å. (2015). Estrogen receptor alpha and beta in health and disease. *Best Practice and Research: Clinical Endocrinology and Metabolism*, *29*(4), 557–568. https://doi.org/10.1016/j.beem.2015.04.008

Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Tunyasuvunakool, K., Bates, R., Žídek, A., Potapenko, A., Bridgland, A., Meyer, C., Kohl, S. A. A., Ballard, A. J., Cowie, A., Romera-Paredes, B., Nikolov, S., Jain, R., Adler, J., … Hassabis, D. (2021). Highly accurate protein structure prediction with AlphaFold. *Nature*, *596*(7873), 583–589. https://doi.org/10.1038/s41586-021-03819-2

Junaidin, Chaerani, S., & Fadla, N. H. (2019). *Stufi Homologi Enzim Tironase (Homo sapiens) dengan Mnegginakan Swis-Model*. *VI*(1), 1–7.

Kalontong, P. K., Safithri, M., & Tarman, K. (2022). Penambatan Molekul Senyawa Aktif Spirulina platensis sebagai Inhibitor TMPRSS2 untuk Mencegah Infeksi SARS-COV-2. *Jurnal Pengolahan Hasil Perikanan Indonesia*, *25*(2), 253–267. https://doi.org/10.17844/jphpi.v25i2.40645

Kamelia, T., & Putri, N. A. R. (2023). Perkembangan Precision Medicine di Indonesia. *Indonesian Journal Chest*, *10*(1), 1–12.

Karina, K., Rosadi, I., Rosliana, I., & Wahyuningsih, K. A. (2019). Studi in Silico: Prediksi Pengaruh Mutasi Titik Gen Vascular Endothelial Growth Factor Receptor-2 (Vegfr2) Terhadap Struktur Sekunder Protein. *Al-Kauniyah: Jurnal Biologi*, *12*(2), 220–228. https://doi.org/10.15408/kauniyah.v12i2.11804

Kemenkes RI.(2019). *Penyakit Kanker di Indonesia Berada Pada Urutan 8 di Asia Tenggara dan Urutan 23 di Asia*. Diakses dari: http://p2p.kemkes.go.id/penyakit-kanker-di-indonesia-berada-pada-urutan-8-di-asia-tenggara-dan-urutan-23-di-asia/

Khan, A., Ashfaq-Ur-Rehman, Junaid, M., Li, C. D., Saleem, S., Humayun, F., Shamas, S., Ali, S. S., Babar, Z., & Wei, D. Q. (2020). Dynamics Insights Into the Gain of Flexibility by Helix-12 in ESR1 as a Mechanism of Resistance to Drugs in Breast Cancer Cell Lines. *Frontiers in Molecular Biosciences*, *6*(January), 1–14. https://doi.org/10.3389/fmolb.2019.00159

Klein, M. E., Parvez, M. M., & Shin, J. G. (2017). Clinical Implementation of Pharmacogenomics for Personalized Precision Medicine: Barriers and Solutions. *Journal of Pharmaceutical Sciences*, *106*(9), 2368–2379. https://doi.org/10.1016/j.xphs.2017.04.051

Kumar, P., & Arya, A. (2018). Ramachandran plot - A simplified approach. *Pathfinder Research and Training Foundation, India*, *January*, 6. https://www.researchgate.net/publication/330158666_Ramachandran_plot-_A_simplified_approach

Kwakowsky, A., Milne, M. R., Waldvogel, H. J., & Faull, R. L. (2016). Effect of estradiol on neurotrophin receptors in basal forebrain cholinergic neurons: Relevance for Alzheimer's disease. *International Journal of Molecular Sciences*, *17*(12), 1–28. https://doi.org/10.3390/ijms17122122

Labellapansa, A., Muhimmah, I., & Indrayanti. (2013). Klasifikasi Citra Imunohistokimia Sel Kanker Payudara HER2 Skore 1+ dan 3+. *Seminar Nasional Informatika Medis (SNIMed) IV*

Laskowski, R. A. (2001). PDBsum: Summaries and analyses of PDB structures. *Nucleic Acids Research*, *29*(1), 221–222. https://doi.org/10.1093/nar/29.1.221

Laskowski, R. A., MacArthur, M. W., Moss, D. S., & Thornton, J. M. (1993). PROCHECK: a program to check the stereochemical quality of protein structures. *Journal of Applied Crystallography*, *26*, 283–291. https://doi.org/10.1107/s0021889892009944

Lewandowska, A. M., Rudzki, M., Rudzki, S., Lewandowski, T., & Laskowska, B. (2019). Environmental risk factors for cancer - review paper. *Annals of Agricultural and Environmental Medicine*, *26*(1), 1–7. https://doi.org/10.26444/aaem/94299

Liang, J., & Shang, Y. (2013). Estrogen and cancer. *Annual Review of Physiology*, *75*(9), 9.1-9.16. https://doi.org/10.1146/annurev-physiol-030212-183708

Liao, P. Y., & Lee, K. H. (2010). From SNPs to functional polymorphism: The insight into biotechnology applications. *Biochemical Engineering Journal*, *49*(2), 149–158. https://doi.org/10.1016/j.bej.2009.12.021

Lovell, S. C., Davis, I. W., Adrendall, W. B., de Bakker, P. I. W., Word, J. M., Prisant, M. G., Richardson, J. S., & Richardson, D. C. (2003). Structure validation by C alpha geomF. *Proteins: Structure, Function, and Genetics*, 437–450. http://onlinelibrary.wiley.com/store/10.1002/prot.10286/asset/10286_ftp.pdf?v=1&t=gwhx9jy0&s=b3b0f129a5acf7f4513aea04d22aad7ee4f4a89d

Lopez, M.J., S. Shamim., Mohiuddin.(2013). Biochemistry, Essential Amino Acids. [*Online*]. Diakses dari https://www.ncbi.nlm.nih.gov/books/NBK557845/

Lu, Y., & Liu, W. (2020). Selective Estrogen Receptor Degraders (SERDs): A Promising Strategy for Estrogen Receptor Positive Endocrine-Resistant Breast Cancer. *Journal of Medicinal Chemistry*, *63*(24), 15094–15114. https://doi.org/10.1021/acs.jmedchem.0c00913

Łukasiewicz, S., Czeczelewski, M., Forma, A., Baj, J., Sitarz, R., & Stanisławek, A. (2021). Breast Cancer—Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies— An Updated Review. *Cancers*, *13*, 1–30.

Luo, J., Wu, M., Gopukumar, D., & Zhao, Y. (2016). Big Data Aplication in Biomedical Research and Health Care : A literature Review. *Biomed Inform Insight*, *8*, 1–10. https://doi.org/10.1051/jphyscol:1981825

Mappa, A. I. D., Arisadewo, L., Anwar, K., & Hasugian, R. A. (2021). Pemanfaatan Big Data dalam Mengangani Data Peningkatan Pasien COVID-19 di Indonesia. *Jurnal Teknik Informatika Unika St. Thomas*, *6*(1), 178–187.

Mardianingrum, R., Bachtiar, K. R., Susanti, S., Aas Nuraisah, A. N., & Ruswanto, R. (2021). Studi In Silico Senyawa 1,4-Naphthalenedione-2-Ethyl-3-Hydroxy sebagai Antiinflamasi dan Antikanker Payudara. *ALCHEMY Jurnal Penelitian Kimia*, *17*(1), 83. https://doi.org/10.20961/alchemy.17.1.43979.83-95

Marshall, S. F., Clarke, C. A., Deapen, D., Henderson, K., Largent, J., Neuhausen, S. L., Reynolds, P., Ursin, G., Horn-Ross, P. L., Stram, D. O., Templeman, C., & Bernstein, L. (2010). Recent breast cancer incidence trends according to hormone therapy use: The California Teachers Study cohort. *Breast Cancer Research*, *12*(1), 1–9. https://doi.org/10.1186/bcr2467

Martaadisoebrata, D. (2019). Personalized Medicine pada Pelayanan Kesehatan Reproduksi Personalized Medicine in Reproductive Health Service. *Obstetrics & Ginecology Science*, *2*(1), 1–13.

Maryanto, B. (2017). Big Data dan Pemanfaatannya Dalam Berbagai Sektor. *Media Informatika*, *16*(2), 14–19. https://jurnal.likmi.ac.id/Jurnal/7_2017/0717_02_BudiMaryanto.pdf

Mathur, R., Rana, B. S., & Jha, A. K. (2018). SNP, single nucleotide polymorphism. *Encyclopedia of Animal Cognition and Behavior*. https://doi.org/https://doi.org/10.1007/978-3-319-47829-6_2049-1

Mayrovitz, H. N. (2022). *Breast Cancer*. Excon Publication: Brisbane

McNutt, A. T., Francoeur, P., Aggarwal, R., Masuda, T., Meli, R., Ragoza, M., Sunseri, J., & Koes, D. R. (2021). GNINA 1.0: molecular docking with deep learning. *Journal of Cheminformatics*, *13*(1), 1–20. https://doi.org/10.1186/s13321-021-00522-2

Menteri Kesehatan RI. (2022). Peraturan Menteri Kesehatan Republik Indonesia Nomor 13 Tahun 2022 Tentang Perubahan Atas Peraturan Menteri Kesehatan Nomor 21 Tahun 2020 Tentang Rencana Strategis Kementerian Kesehatan Tahun 2020-2024. https://peraturan.bpk.go.id/Home/Download/212694/Permenkes Nomor 13 Tahun 2022.pdf

Morihito, R. V. S. ., Chungdinata, S. E., Nazareth, T. A., Pulukadang, M. I., Makalew, R. A. ., & Pinontoan, B. (2017). Identifikasi Perubahan Struktur Dna Terhadap Pembentukan Sel Kanker Menggunakan Dekomposisi Graf. *Jurnal Ilmiah Sains*, *17*(2), 153. https://doi.org/10.35799/jis.17.2.2017.17368

Movérare-Skrtic, S., Börjesson, A. E., Farman, H. H., Sjögren, K., Windahl, S. H., Lagerquist, M. K., Andersson, A., Stubelius, A., Carlsten, H., Gustafsson, J. Å., & Ohlsson, C. (2014). The estrogen receptor antagonist ICI 182,780 can act both as an agonist and an inverse agonist when estrogen receptor α AF-2 is modified. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(3), 1180–1185. https://doi.org/10.1073/pnas.1322910111

Muhammed, M. T., & Aki-Yalcin, E. (2022). Molecular Docking: Principles, Advances, and its Applications in Drug Discovery. *Letters in Drug Design & Discovery*, *19*, 1–16. https://doi.org/10.2174/1570180819666220922103109

Naithani, N., Sinha, S., Misra, P., Vasudevan, B., & Sahu, R. (2021). Precision medicine: Concept and tools. *Medical Journal Armed Forces India*, *77*(3), 249–257. https://doi.org/10.1016/j.mjafi.2021.06.021

Nathan, M. R., & Schmid, P. (2017). A Review of Fulvestrant in Breast Cancer. *Oncology and Therapy*. https://doi.org/10.1007/s40487-017-0046-2

National Institutes of Health (US); Biological Sciences Curriculum Study. NIH Curriculum Supplement Series Bethesda (MD): National Institutes of Health (US). (2007). *Understanding Cancer*. Diakses dari https://www.ncbi.nlm.nih.gov/books/NBK20362/

Nicoloso, M. S., Sun, H., Spizzo, R., Kim, H., Wickramasinghe, P., Shimizu, M., Wojcik, S. E., Ferdin, J., Kunej, T., Xiao, L., Manoukian, S., Secreto, G., Ravagnani, F., Wang, X., Radice, P., Croce, C. M., Davuluri, R. V., & Calin, G. A. (2010). Single-nucleotide polymorphisms inside microRNA target sites influence tumor susceptibility. *Cancer Research*, *70*(7), 2789–2798. https://doi.org/10.1158/0008-5472.CAN-09-3541

Nurmayeni, & Windarti, I. (2022). Gambaran Subtipe Molekuler Kanker Payudara di Indonesia. *Agromedicine*, *9*(5), 145–148.

Osborne, C. K., Wakeling, A., & Nicholson, R. I. (2004). Fulvestrant: An oestrogen receptor antagonist with a novel mechanism of action. *British Journal of Cancer*, *90*, S2–S6. https://doi.org/10.1038/sj.bjc.6601629

Pagadala, N. S., Syed, K., & Tuszynski, J. (2017). Software for molecular docking: a review. *Biophysical Reviews*, *9*(2), 91–102. https://doi.org/10.1007/s12551-016-0247-1

Park, S. H., Jung, I. K., & Kim, J. H. (2020). Effect of dietary changes from high-fat diet to normal diet on breast cancer growth and metastasis. *Journal of Nutrition and Health*, *53*(4), 369–380. https://doi.org/10.4163/JNH.2020.53.4.369

Patel, A. (2020). Benign vs Malignant Tumors. *JAMA Oncology*, *6*(9), 1488. https://doi.org/10.1001/jamaoncol.2020.2592

Pham, T. H., Lecomte, S., Efstathiou, T., Ferriere, F., & Pakdel, F. (2019). An update on the effects of glyceollins on human health: Possible anticancer effects and underlying mechanisms. *Nutrients*, *11*(1). https://doi.org/10.3390/nu11010079

Pradana, M. S., Apsari, G. R., Adawiyah, R., Linatari, M. A., & Rahmayadi, D. (2019). Program Pengajaran Sequence Alignment Berbasis Bioinformatika di MA Matholi'ul Anwar Lamongan. *Jurnal Pengabdian Kepada Masyarakat*, *3*(1), 101–106.

Prieto-Martínez, F. D., Arciniega, M., & Medina-Franco, J. L. (2018). Acoplamiento Molecular: Avances Recientes y Retos. *TIP Revista Especializada En Ciencias Químico-Biológicas*, *21*, 65–87. https://doi.org/10.22201/fesz.23958723e.2018.0.143

Purba, E. F., & Simanjuntak, P. (2012). *Metode Penelitian*. Percetakan SADIA: Medan

Puspawati, P. R., Kristina, S. A., & Wiedyaningsih, C. (2020). Dampak merokok terhadap kematian dini akibat kanker di Indonesia: estimasi years of life lost (YLL). *J Majalah Farmaseutik*, *16*(1), 104. https://doi.org/10.22146/farmaseutik.v16i1.49790

Rafeeq, M. M. (2022). Molecular docking analysis of phytochemicals with estrogen receptor alpha. *Bioinformation*, *18*(8), 697–702. https://doi.org/10.6026/97320630018697

Rahayu, Y. C., & Auerkari, E. (2004). Teknik Immuno Histokimia Sebagai Pendeteksi Penyakit Infeksi. *Jurnal Kedokteran Gigi Universitas Indonesia*, *11*(2), 76–82.

Rahmadhayanti, E., Hayati, L., & Saleh, M. (2014). Hubungan polimorfisme gen reseptor angiotensin II tipe 1 1166 A/C dengan kejadian preeklampsia. *Jurnal Kedokteran*, *46*(1), 52–58.

Reynaldi, M. A., & Setiawansyah, A. (2022). Potensi anti-kanker payudara tanaman songga (Strychnos lucida R.Br): Tinjauan interaksi molekuler terhadap reseptor estrogen-α in silico. *Sasambo Journal of Pharmacy*, *3*(1), 30–35. https://doi.org/10.29303/sjp.v3i1.149

Robertson, J. F. R., Come, S. E., Jones, S. E., Beex, L., Kaufmann, M., Makris, A., Nortier, J. W. R., Possinger, K., & Rutqvist, L. E. (2005). Endocrine treatment options for advanced breast cancer - The role of fulvestrant. *European Journal of Cancer*, *41*(3), 346–356. https://doi.org/10.1016/j.ejca.2004.07.035

Robertson, J. F. R., & Harrison, M. (2004). Fulvestrant: Pharmacokinetics and pharmacology. *British Journal of Cancer*, *90*, S7–S10. https://doi.org/10.1038/sj.bjc.6601630

Robinson, M., Atmakusumah, T. D., Irawan, C., & Shatri, H. (2019). Immunohistochemistry Profile of Breast Cancer Patients that Get Anthracyclin – Based Chemotherapy in RSUD Kota Bogor. *Jurnal Penyakit Dalam Indonesia*, *6*(4), 173–177.

Sadée, W., & Dai, Z. (2005). Pharmacogenetics/genomics and personalized medicine. *Human Molecular Genetics*, *14*(2), 207–214. https://doi.org/10.1093/hmg/ddi261

Saini, A., Kumar, M., Bhatt, S., Saini, V., & Malik, A. (2020). Cancer Causes and Treatment. *Internation Journal of Pharmaceutical Sciences and Research*, *11*(7), 3109–3122. https://doi.org/10.13040/IJPSR.0975-8232.11(7).3109-22

Saragih, R. Y., Hidayah, N., & Roza, D. (2021). Docking Molekular Potensi Antikanker Payudara Protein3ert Dengan Senyawa Turunan Kuinin. *Prosiding Seminar Nasional Kimia & Pendidikan Kimia*, 376–381.

Sari, S. E., Harahap, W. A., & Saputra, D. (2018). Pengaruh Faktor Risiko Terhadap Ekspresi Reseptor Estrogen Pada Penderita Kanker Payudara Di Kota Padang. *Jurnal Kesehatan Andalas*, *7*(4), 461. https://doi.org/10.25077/jka.v7.i4.p461-468.2018

Saudale, F. Z. (2020). Pemodelan Homologi Komparatif Struktur 3d Protein dalam Desain dan Pengembangan Obat. *Al-Kimia*, *8*(1), 93–103. https://doi.org/10.24252/al-kimia.v8i1.9463

Scabia, V., Ayyanan, A., De Martino, F., Agnoletto, A., Battista, L., Laszlo, C., Treboux, A., Zaman, K., Stravodimou, A., Jallut, D., Fiche, M., Bucher, P., Ambrosini, G., Sflomos, G., & Brisken, C. (2022). Estrogen receptor positive breast cancers have patient specific hormone sensitivities and rely on progesterone receptor. *Nature Communications*, *13*(1). https://doi.org/10.1038/s41467-022-30898-0

Setiawan, H., & Irawan, M. I. (2017). Kajian Pendekatan Penempatan Ligan Pada Protein Menggunakan Algoritma Genetika. *Jurnal Sains Dan Seni ITS*, *6*(2), 2–6. https://doi.org/10.12962/j23373520.v6i2.25468

Setiawan, I. M. A. (2023). Peran Pemeriksaan Imunohistokimia dalam Diagnosis dan Prognosis Kanker Payudara. *Cermin Dunia Kedokteran. 50*(8), 443–446.

Shah, R., Rosso, K., & David Nathanson, S. (2014). Pathogenesis, prevention, diagnosis and treatment of breast cancer. *World Journal of Clinical Oncology*, *5*(3), 283–298. https://doi.org/10.5306/wjco.v5.i3.283

Shatoff, E., & Bundschuh, R. (2020). Single nucleotide polymorphisms affect RNA-protein interactions at a distance through modulation of RNA secondary structures. *PLoS Computational Biology*, *16*(5), 1–16. https://doi.org/10.1371/journal.pcbi.1007852

Shen, L. X., Basilion, J. P., & Stanton, J. (1999). Single-nucleotide polymorphisms can cause different structural folds of mRNA. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(14), 7871–7876. https://doi.org/10.1073/pnas.96.14.7871

Shiovitz, S., & Korde, L. A. (2015). Genetics of breast cancer: a topic in evolution. *Annals of Oncology*. *26*(7), 1291–1299.

Singh, V. ., Singh, A. ., Chand, R., & Kushwaha, C. (2011). Role of Bioinformatics in Agriculture and Sustainable Development. *International Journal of Bioinformatics Research*, *3*(2), 221–226. https://doi.org/10.1007/978-3-031-01949-4_44

Sinha, T. (2018). Tumors: Benign and Malignant. *Cancer Therapy & Oncology International Journal*, *10*(3), 1–3. https://doi.org/10.19080/ctoij.2018.10.555790

Soen, G. I. E., Marlina, & Renny. (2022). Implementasi Cloud Computing dengan Google Colaboratory Pada Aplikasi Pengolah Data Zoom Participants. *Journal Informatic Technology And Communication*, *6*(1), 24–30.

Suhara.(2018). *Dasar-dasar Biokimia*. Prisma Press: Bandung

Sulaiman, T. W., Fitriansyah, R. B., Alaudin, A. R., & Ratsanjani, M. H. (2023). Penerapan Big Data Dalam Kesehatan Masyarakat. *Jurnal Sains, Teknik, Dan Studi Kemasyarakatan*, *1*(3), 129–138.

Sun, Z., Shi, Y., Shen, Y., Cao, L., Zhang, W., & Guan, X. (2015). Analysis of different HER-2 mutations in breast cancer progression and drug resistance. *Journal of Cellular and Molecular Medicine*, *19*(12), 2691–2701. https://doi.org/10.1111/jcmm.12662

Sunarto, A. A. (2015). Perbandingan Program Sequence Alignment. *Jurnal Rekayasa Nusaputra*, *1*(1), 1–6

Syahputra, G., Ambarsari, L., & Sumaryada, T. (2014). Simulasi Docking Kurkumin Enol, Bisdemetoksikurkumin dan Analognya sebagai Inhibitor Enzim12-Lipoksigenase. *Jurnal Biofisika*, *10*(1), 55–67.

Teng, S., Madej, T., Panchenko, A., & Alexov, E. (2009). Modeling effects of human single nucleotide polymorphisms on protein-protein interactions. *Biophysical Journal*, *96*(6), 2178–2188. https://doi.org/10.1016/j.bpj.2008.12.3904

Torres, P. H. M., Sodero, A. C. R., Jofily, P., & Silva-Jr, F. P. (2019). Key topics in molecular docking for drug design. *International Journal of Molecular Sciences*, *20*(18), 1–29. https://doi.org/10.3390/ijms20184574

Toy, W., Shen, Y., Won, H., Green, B., Sakr, R. A., Will, M., Li, Z., Gala, K., Fanning, S., King, T. A., Hudis, C., Chen, D., Taran, T., Hortobagyi, G., Greene, G., Berger, M., Baselga, J., & Chandarlapaty, S. (2013). ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. *Nature Genetics*, *45*(12), 1439–1445. https://doi.org/10.1038/ng.2822

Triwani, T., & Saleh, I. (2015). Single Nucleotide Polymorphism Promoter -765g / C Gen Cox-2 Sebagai Faktor Risiko Terjadinya Karsinoma Kolorektal. *Biomedical Journal of Indonesia*, *1*(1), 2–10.

Trott, O., & Olson, A. J. (2010). Software News and Updates Gabedit — AutoDock Vina: Improving the Speed and Accuracy of Docking with a New Scoring Function, Efficient Optimization, and Multithreading. *Journal of Computational Chemistry*, *31*(2), 455–461. https://doi.org/10.1002/jcc

Tsunoda, D. F., Freitas, A. A., & Lopes, H. S. (2011). A genetic programming method for protein motif discovery and protein classification. *Soft Computing*, *15*(10), 1897–1908. https://doi.org/10.1007/s00500-010-0624-9

Tyagi, N., Sharma, G. N., Shrivastava, B., & Chaudhary, N. (2017). *An International Open access peer reviewed journal Cancer : An Overview Article Information :* *6*(5), 2740–2747.

Vinsentricia, A., Hami Seno, D. S., & Bintang, M. (2015). *In Silico* Analysis of *Curcuma longa* Against PCAF Histon Asetiltransferase. *Current Biochemistry*, *2*(2), 52–62. https://doi.org/10.29244/cb.2.2.52-62

Wadood, A., Ahmed, N., Shah, L., Ahmad, A., Hassan, H., & Shams, S. (2013). In-silico drug design: An approach which revolutionarised the drug discovery process. *OA Drug Design and Delivery*, *1*(1), 1–4. https://doi.org/10.13172/2054-4057-1-1-1119

Wibawa., I. D. N. (2017). Personalized medicine in Gastroentero-hepatology. *Denpasar Update in Gastroentero-Hepatology*, 4-9

Widyastuti, M. D., Noviyanti, N. K. M., Sanjaya, I. K. N. S., & Susanti, N. M. P. (2020). Aktivitas Antihiperpigmentasi Likopen Secara in Silico. *Jurnal Kimia*, *14*(2), 107. https://doi.org/10.24843/jchem.2020.v14.i02.p01

Yaşar, P., Ayaz, G., User, S. D., Güpür, G., & Muyan, M. (2017). Molecular mechanism of estrogen–estrogen receptor signaling. *Reproductive Medicine and Biology*, *16*(1), 4–20. https://doi.org/10.1002/rmb2.12006

Yuan, S., Chan, H. C. S., & Hu, Z. (2017). Using PyMOL as a platform for computational drug design. *Wiley Interdisciplinary Reviews: Computational Molecular Science*, *7*(2), 1–10. https://doi.org/10.1002/wcms.1298

Zardecki, C., Dutta, S., Goodsell, D. S., Voigt, M., & Burley, S. K. (2016). RCSB Protein Data Bank: A Resource for Chemical, Biochemical, and Structural Explorations of Large and Small Biomolecules. *Journal of Chemical Education*, *93*(3), 569–575. https://doi.org/10.1021/acs.jchemed.5b00404

Zhang, C., Guo, S., Yang, L., Liu, J., Zheng, S., Zhong, Q., Zhang, Q., & Wang, G. (2017). Metabolism, pharmacokinetics, and bioavailability of ZB716, a Steroidal Selective Estrogen Receptor Downregulator (SERD). *Oncotarget*, *8*(61), 103874–103889. https://doi.org/10.18632/oncotarget.21808