DAFTAR PUSTAKA

Attia, A., 2005, Why should researchers report to confidence interval in modern research? *Middle East Fertility Society Journal*, *10*(1), 78–81.

Badran, Z., Gaudin, A., Struillou, X., Amador, G., and Soueidan, A., 2020, Periodontal Pockets: A Potential Reservoir for SARS-CoV-2?, *Medical Hypotheses,* 143: 109907.

Bertolini, M. , Pita, A., Koo, S., Cardenas, A., and Meethil, A., 2020, Periodontal Disease in the COVID-19 Era: Potential Reservoir and Increased Risk for SARS–CoV-2, *Pesqui. Bras. Odontopediatria Clín. Integr*. 2020; 20(supp1):e0140.

Brooks, G., Carroll, K. C., Butel, J., dan Morse, S. 2012. Jawetz, Melnick & Adelberg's Medical Microbiology (26th ed.). New York: McGraw-Hill Medical.

Cai, H., 2020. Sex Difference And Smoking Predisposition In Patients With COVID-19. *Lancet Respir Med*, (20)30117-X 42.

Conforti, C., Giuffrida, R., Dianzani, C., Di Meo, N., Zalaudek, I., 2020, COVID-19 and psoriasis: Is it time to limit treatment with immunosuppressants? A call for action. *Dermatol Ther*:e13298.

De Wit. E, Van Doremalen, N., Falzarano, D., Munster, V.J., 2016, SARS and MERS: Recent insights into emerging coronaviruses. *Nat Rev Microbiol*;14(8):523–34.

Departemen Kesehatan Republik Indonesia. 2011. *Laporan Survey Kesehatan Rumah Tangga (SKRT)*. Jakarta. Badan Litbangkes.

Dingsdag, S. , Nelson S., dan Coleman N.V., 2016. Bacterial communities associated with apical periodontitis and dental implant failure. *Microb Ecol Health Dis*. Nov 8; 27:31307.

Dingsdang, S.A., dan Hunter, N., 2018. Metronidazole: an update on metabolism, structure-cytotoxicity and resistance mechanisms.*J Antimicrob Chemother*. Feb 1;73(2):265-279.

Du., X., Li., Y., ,Xia, Y.L., Ai, S.M., Liang, J., Sang, P., Ji,X., dkk. 2016. Insights into Protein–Ligand Interactions: Mechanisms, Models, and Methods.*Int J Mol Sci.* 2016 Feb; 17(2): 144.

Ehlers, M., Grotzinger, J., Fisher, M., Bos, H.K., Brakenhoff J.P.J., John, S.R., . (1996). Identification of Single Amino Acid Residues of Human IL-6 Involved in Receptor Binding and Signal Initiation. *Journal of Interferon & Cytokine Research*, 16(8), 569–576.

Fang ,L., Karakiulakis, G., Roth, M., 2020. Are Patients With Hypertension And Diabetes Mellitus At Increased Risk For COVID-19 Infection? *Lancet Respir Med*, (20)30116-8

Gharebaghi, R., Heidary, F., Moradi, M., and Parvizi, M., 2020, Metronidazole: A Potential Novel Addition to the COVID- 19 Treatment Regimen, *Archives of Academic Emergency Medicine*, 8(1): e40.

Gorbalenya, A.E., Baker, S.C., Baric, R.S., de Groot, R.J., Drosten, C., Gulyaeva, A.A., 2020, Severe acute respiratory syndrome-related coronavirus : The species and its viruses – a statement of the Coronavirus Study Group. *BioRxiv*.

Han, Y., and Yang, H., 2020, The transmission and diagnosis of 2019 novel coronavirus infection disease (COVID-19): A Chinese perspective, *J Med Virol*, Jun;92(6):639-644.

Hariono M., Nuwarda R.F., Yusuf M., Rollando R, Jenie R.I. , Al-najjar B.., 2020, Arylamide as Potential Selective Inhibitors for Matrix Metalloproteinase 9 (MMP9): Design, Synthesis, Biological Evaluation and Molecular Modeling *J. Chem. Inf. Model*, 60, 1, 349–359

Hevener, K., Zhao, W., Ball, D., Babaoglu, K., Qi, J.J., White, S., dan Lee, R. 2009. Validation of molecular docking programs for virtual screening against dihydropteroate synthase. *J of Chemical Information and Modeling*. 46(2):444-460.

Kawiyana, S. 2014. Interleukin-6 Yang Tinggi Sebagai Faktor Risiko Terhadap Kejadian Osteoporosis Pada Wanita Pascam Enopause Defisiensi Estrogen. *Journal of Internal Medicine*. Vol 10. No. 10.

Li, Z., Yi, Y., Luo, X., Xiong, N., Liu, Y., Li, S., Sun, R., Wang, Y., Hu., B., Chen, W., Zhang, Y., Wang, J., Huang, B., Lin, Y., Yang, J., Cai, W., Wang, X., Cheng, J., Chen, Z., Sun, K., Pan, W., Zhan, Z., Chen, L. Ye, F., 2020, Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis, *J Med Virol*, Sep;92(9):1518-1524.

Liang,W., Guan, W., Chen, R., Wang, W., Li, J., Xu, K., 2020, Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*;21(3):335-7.

Liu, B., Li, M., Zhou, Z., Guan, X., and Xiang, F., 2020, Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)?, *J Autoimmun*, 111 :102452

Löfmark, S., Edlund, C., and Nord, C.E., 2009, Metronidazole is Still the Drug of Choice for Treatment of Anaerobic Infections. *CID (Clinical Infectious Disease)*, 50:1.

Marcou, G., dan Rognan, D., 2007. Optimizing fragment and scaffold docking by use of Molecular Interaction Fingerprints. *Journal of Chemical Information and Modeling*, 47(1), 195-207.

Masfufatun, P.O.A., Tania, L., dan Hariyanto, A. B., 2018, Kadar IL-6 dan IL-10 Serum pada Tahapan Inflamasi di Rattus norvegicus yang terinfeksi Candida albicans, *Jurnal Kedokteran Brawijaya* 30 (1), 19-23.

Molayem, S., and Pontes, C., 2020, The Mouth-COVID Connection: Il-6 Levels in Periodontal Disease — Potential Role in COVID-19-Related Respiratory Complication, *J Calif Dent Assoc*, 7:1-44.

Morris, dkk. (2009), *User Guide AutoDock Version 4.2, Updated for version 4.2.5, Automated Docking of Flexible Ligands to Flexible Receptors*. The Scripps Research Institute, USA

Newman, M. G., Takei, H. H., Klokkevold, P. R., Carranza, F. A., 2019, *Clinical Periodontology 13th Ed*, Phildelphia:Elsevier Saunders.

Perhimpunan Dokter Paru Indonesia, 2020, *Panduan Praktik Klinis: Pneumonia 2019-nCoV*, PDPI: Jakarta.

Putri, M.H.. 2009. *Ilmu Pencegahan Penyakit Jaringan Keras dan Jaringan Pendukung Gigi.* Jakarta: EGC. p. 56, 75.

Riedel S., Morse, S.A., Mietzner, T., and Miller, S., 2019, *Medical Microbiology*. 28th ed. New York: McGrawHill Education/Medical.

Sakaguchi, W. , Kubota, N., Shimizu, T., Saruta, J., Fuchida, S., Kawata, A., Yamamoto, Y., Sugimoto , M., Yakeishi, M. dan Tsukinoki, K., 2020, Existence of SARS-CoV-2 Entry Molecules in the Oral Cavity, *Int. J. Mol. Sci.*, 21, 6000.

Setiawati, A., Riswanto, F.D.O., Yuliani, S.H., Istyastono, E.P., 2014, Retrospective Validation of A Structure-Based Virtual Screening Protocol To Identify Ligands For Estrogen Receptor Alpha and Its Application To Identify The Alpha-Mangostin Binding Pose, *Indo J. Chem*, 14(2), 103-108.

Sixou, J.L., Magaud, C., Gougeon, AJ., Cormier, M., dan Mallet, M.B., 2003. Microbiology of mandibular third molar pericoronitis: incidence of beta-lactamase-producing bacteria. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* Jun; 95(6):655-9.

Soriano, V., Barreiro, P., 2020, Impact of New Coronavirus Epidemics on HIV-Infected Patients. *AIDS Rev*;22(1):57-8.

Taize, C.N., Maria, C.. 2006. *Factors Related to Periodontal Disease in a Rural Population. Brazilian Oral Research*. Sao paulo vol 20 no 3., pp 74- 88.

Tania, P.O.A., Simamora, D., Parmasari, W.D., dan Rahmawati, F., 2014, Kadar Interleukin 6 (IL-6) sebagai Indikator Progresivitas Penyakit Reumatoid Arthritis (RA), 2014, Jurnal Ilmiah Kedokteran, Vol.1:III, Maret.

Tjay, T. H., dan Rahardja, K., 2002, Obat-Obat Penting, Khasiat, Penggunaan dan Efek Sampingnya, Edisi Kelima, 270-279, Efek Media Komputindo, Jakarta

Wang, C., Horby, P. W., Hayden, F. G., and Gao, G. F., 2020, A Novel Coronavirus Outbreak of Global Health Concern. *Lancet,* 395:470–473.

WHO, 2020, WHO Director-General's Remarks at The Media briefing on 2019-nCov.

Wishart, D.S., Feunang, Y.D., Guo, A.C., Lo, E.J., Marcu, A., Grant, J.R., Sajed, T., Johnson D., Li, C., Sayeeda, Z., Assempour, N., Iykkaran, I., Liu., Y., Maciejewski, A., Gale, N., Wilson, A., Chin, L., Cummings, R., Le, D., Pon, A., Knox, C., Wilson, M., 2017, Drug Bank 5.0: major update to the DrugBank database for 2018. Nucleic Acids Res. 2017 Noc 8. doi: 10.1093/nar/gkx1037. Diakses tanggal 20 Juli 2021.

Xia, Y., Jin, R., Zhao, J., Li, W., Shen, H., 2020, Risk of COVID-19 for cancer patients. *Lancet Oncol*.(20)30150-9.

Xu, Z., 2020, Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Resp. Med*. 8, 420–422.

Zhang, L., Jackson, C.B., Mou, H., Ojha, A., Peng, H., Quinlan, B.D., Rangarajan, E.S., Pan, A., Vanderheiden, A., Suthar, M.S., Li, W., Izard, T., Rader, C., Farzan, M., Choe, H., 2020, SARS-CoV-2 spike-protein D614G mutation increases virion spike density and infectivity, *Nat Commun*, Nov 26;11(1):603.

Zhou, P., 2020, A Pneumonia Outbreak Associated with a New Coronavirus of Probable Bat Origin. *Nature*, 579:270-273.

LAMPIRAN

Lampiran 1. Protokol Penelitian dan Protokol Post Docking

```
Preparasi Ligand
Menggambar struktur metronidazol di aplikasi marvinSketch
simpan dalam bentuk file Metronidazol.mol2
Buka discovery studio 3.5 dan buka metronidazol.mol2
select ligand kemudian chemistry add hidrogen
save as Metronidazol_01.pbd
buka file di autodocktools
ligand > input> open > all files > Metronidazol_01.pdb
ligand > output> save as pdbqt > Metronidazol_01.pdbqt

Preparasi Protein 7dc8
Download protein reseptor IL-6 di RCSB (dalam bentuk polimer)
Download 7dc8 dalam bentuk pdb format https://www.rcsb.org/structure/7dc8
Buka file di aplikasi discovery studio
kemudian view hierachy
Hapus bagian B,C,D, air, hetatm, ligand co kristal
simpan file dalam benuk 7dc8.pdb


Menentukan Titik koordinaat binding pocket dengan PLANTS 1.2 dan SPORES

cd programs
wget http://www.tcd.uni-
    konstanz.de/plants_download/download/PLANTS1.2_64bit
wget http://www.tcd.uni-konstanz.de/plants_download/download/SPORES_64bit
chmod u+x PLANTS1.2_64bit SPORES_64bit
cd ..
mkdir Docking1
cd Docking1
wget https://files.rcsb.org/download/7dc8.pdb
~/programs/SPORES_64bit --mode splitpdb 7dc8.pdb
~/programs/PLANTS1.2_64bit --mode bind ligand_ATP301_0.mol2 5
    protein.mol2
cp ligand_ATP301_0.mol2 ligand.mol2
conda activate adt
~/miniconda3/envs/adt/bin/prepare_receptor4.py -r protein.mol2
~/miniconda3/envs/adt/bin/prepare_ligand4.py -l ligand.mol2
conda deactivate
cd

Penambatan Molekul menggunakan autodocktools

Buat folder bernama metronidzole_01
Pindahkan file 7dc8.pdb Metronidazol_01.pdbqt Metronidazol_01.pdb dalam
    folder ini
pada linux panggil aplikasi autodocktools /autodocktools
pada aplikasi autodocktools
file > read molecule > 7dc8.pdb
edit > charge > kollman > oke
Grid > macromolecule > choose > select 7dc8 > oke > 7dc8.pdbqt
Grid > set map type > open ligand > Metronidazol_01.pdbqt
Grid > grid box > x = 9.986; y = 23.091; z = 20.634
Grid > output > save gpf > Metronidazol_01.gpf
Docking > macromolecule > set rigid filename > 7dc8.pdbqt
Docking > ligand > choose > Metronidazol_01 > select > accept
Docking > search parameters > genetic alogritm > set GA 1000
Docking > docking parameter > accept
```

```
Docking > output > lamarcian > Metronidazol_01.dpf > save
Pada linux buka terminal
ketik cd ~/Metronidazol_01
ls
autogrid4 -p Metronidazol_01.gpf -l Metronidazol_01.glg&
tail -f Metronidazol_01.glg

cd ~/Metronidazol_01
autodock4 -p Metronidazol_01.dpf -l Metronidazol_01.dlg&
tail -f Metronidazol_01.dlg

Buka file Metronidazol_01.dlg pada wordpad
Ctrl + F, lalu ketik “histogram”
Posisi ikatan ligan-protein paling stabil jika:
Energy paling kecil.
Jumblah anggota cluster paling banyak
Pilih cluster dengan anggota terbanyak. Perhatikan angka run-nya
Buka autodocktools.
Analyze lalu docking kemudian open.
Select file dlg lalu open
Analyze lalu conformation kemudian play
Masukan angka 368 dan 216 lalu klik &
Pilih write current simpan 7dc8_02 docking pose 216.pdbqt 7dc8_02 docking
    pose 368.pdbqt
Buka discovery studio 3,5 client
Buka file docking pose 216.pdbqt dan 7dc8_02 docking pose 368.pdbqt
buka file protein 7dc8.pdb
copy struktur 7dc8_02 docking pose 216 dan docking pose 368.pdbqt ke file
    protein 7dc8
Klik scripts lalu ligan kemudian interaction show ligan binding site atom
Simpan hasil visualisasi
```