In Silico Study of Tyramine-Fe Complex in Brotowali (*Tinospora crispa*) as Anti-Inflammatory

Wimbuh Tri Widodo
Department of Biology, Faculty of Mathematics and Natural Sciences,
Brawijaya University
STIKes Karya Putra Bangsa
Tulungagung Indonesia
wimbuhtriwidodo@gmail.com

Sri Widyarti and Sutiman Bambang Sumitro
Department of Biology, Faculty of Mathematics and Natural Sciences,
Brawijaya University
swid@ub.ac.id, sutiman@ub.ac.id

Djoko Herry Santjojo
Department of Physics, Faculty of Mathematics and Natural Sciences,
Brawijaya University
dsantjojo@ub.ac.id

Abstract
Tyramine-Fe complex is predicted present in Brotowali (*Tinospora crispa*) and play a role in its anti-inflammatory activity. Excessive inflammation in COVID-19 patients can be fatal and can even cause death. Anti-inflammatory drugs such as aspirin and ibuprofen inhibits the reaction of prostaglandin formation from COX 2 and arachidonic acid. This study aims to investigate COX 2-tyramine-Fe complex interactions using bioinformatic softwares In this study, docking simulations was performed between COX 2 and tyramine-Fe complex, tyramine, ibuprofen, and aspirin. The results showed that COX 2-tyramine-Fe complex binding site overlapped with the COX 2-ibuprofen binding site while COX 2-tyramine binding site overlapped with the COX 2-Aspirin binding site. COX 2-tyramine-Fe complex's binding energy is smaller than COX 2- tyramine, COX 2- aspirin, COX 2-ibuprofen. These results suggest that the COX 2-tyramine-Fe complex has anti-inflammatory properties so that it can prevent excessive inflammation in COVID-19 patients.

Keywords: Tyramine-Fe Complex, Anti-Inflammatory, Brotowali, *Tinospora crispa*.

1. Introduction
Excessive and uncontrolled release of a pro-inflammatory factor in COVID-19 patients causes severe damage to the lung and manifests acute respiratory distress syndrome (ARDS) (Shang et al.), resulting in high mortality (Guan et al.). Inflammation is part of the complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants (Ferrero-Miliani et al.; Fleit). The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and initiate tissue repair. However, progressive inflammation can cause certain unwanted diseases, such as fever, periodontitis, atherosclerosis, rheumatoid arthritis, and cancer (Chen et al.).

Aspirin and ibuprofen are widely used as anti-inflammatory drugs. Both are included in the class of Nonsteroidal Anti-inflammatory Drugs (NSAIDs). NSAIDs block the reaction between arachidonic acid and COX enzymes so that the production of prostaglandins, which are inflammatory mediators, decreases (Ricciotti and Fitzgerald). Non-steroidal anti-inflammatory drugs (NSAIDs) are drugs that are often prescribed by doctors and are sold freely in the community. In the United States and Western Europe, NSAID prescribing reaches up to 4% -7%; however, data on NSAID use in Indonesia have not been obtained. NSAIDs are often used because of their good effectiveness as an

analgesic, anti-inflammatory, and antipyretic. The effectiveness of NSAIDs is derived from their ability to inhibit prostaglandin synthesis by inhibition of the cyclooxygenase enzyme's action. hence arachidonic acid cannot be converted to prostaglandins and thromboxanes (Davis et al.). However, continuous consumption of anti-inflammatory drugs causes side effects (Wongrakpanich et al.). It is necessary to explore alternative anti-inflammatory compounds that have little side effects. One of the compounds that have anti-inflammatory activity is alkaloids (Souto et al.). Alkaloids are widely contained in plants.

Brotowali (Tinospora crispa) is a plant from the Menispermaceae family spread in tropical and subtropical areas. Brotowali can live in the lowlands to the highlands with an altitude of 1,000 m above sea level. Soil types suitable for brotowali growth are clay soil with a pH of 5-7, temperature 25-37^0 C, moderate humidity, rainfall 1,500-3,000 mm / year with a sun intensity of 70-100% (Bebet and Mindarti). Brotowali is a climbing plant (liana), twists to the right, and stems/twigs' arrangement forms a spiral. Young stems are green, smooth, and hairless. The old stem is brownish in color and has lumps (rash). Brotowali has a single leaf, stemmed, heart-shaped, or slightly round like an egg with a sharp tip, 7-12 cm long, 5-10 cm wide. Leaves smooth, 5-15 cm long. Brotowali has flowers classified as small compound flowers, yellow or greenish-yellow (Ahmad et al.). As seen at the figure 1.

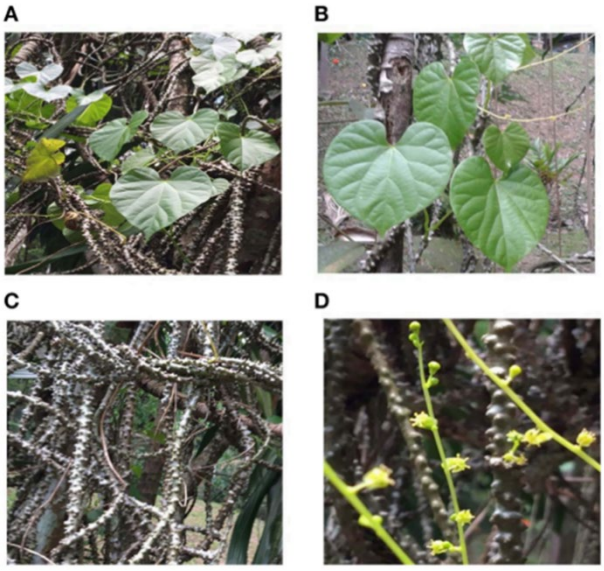

Figure 1. A. Brotowali; B. Brotowali leaves; C. Brotowali trunk. D. Brotowali flowers

Brotowali (Tinospora crispa) is an herbal medicine that contains flavonoids, terpenoids, alkaloids, lignans, nucleosides, and sterols. Besides that, brotowali also has bitter compounds (tinosporine, tinosporic acid, and tinosporol), which is only found in brotowali (Sharma et al.) see figure 1. The various compounds content of brotowali is closely related to its pharmacological activity. (Ahmad et al.). Brotowali is widely used by traditional communities in various countries, including in Indonesia (Pathak et al.; Dweck and Cavin J. P.), Malaysia (Rahman et al.), Thailand (Rungruang and Boonmars), Philippines (Quisumbing) and several other countries that have tropical and sub-tropical climates. Several studies have proven that brotowali has anti-inflammatory activity (Kamarazaman et al.; Hipol et al.), so it can be used as an alternative to NSAIDs. One of the active compounds brotowali from the alkaloids group is tyramine. The physiological effects of tyramine were similar to those of adrenaline (Youdim). Tyramine caused an increase in the mean arterial blood pressure (MAP) and the heart rate (HR) (Praman et al.).

Tyramine and Fe in brotowali are predicted to form a bioinorganic complex. Several studies have shown that the transition metals present in plants can form bioinorganic complexes. Sukmaningsih et al. (2018) proved that the flavonoid complex with Fe was formed in java plum (Syzygium cumini). Capo et al. (2017) prove that the oleuropein complex with copper is also found in the leaves, stems, and processed products of olives (Olea europea).

COX 2 (cyclooxygenase-2), also known as prostaglandin-endoperoxide synthase 2, is an enzyme that catalyzes the reaction of prostaglandin formation from arachidonic acid during infection (Zarghi and Arfaei). Cyclooxygenase, often known as COX, is a family of myeloperoxidase, located on the luminal side of the endoplasmic reticulum and

the nuclear membrane (Diederich et al.). This enzyme catalyzes the biosynthesis of prostaglandins from arachidonic acid (Zarghi and Arfaei; Dandekar et al.). Cyclooxygenase acts in two reactions. The first reaction is converting arachidonic acid released from the plasma membrane by phospholipase-A2 to prostaglandin (PG) G2. The second reaction is the conversion of PGG2 to PGH2. Furthermore, different synthetase enzymes converting PGH2 to prostaglandins D2, F2α, E2, I2 and thromboxane A2. Prostanoids (prostaglandins and thromboxane) are released within a short period from cells, where they act locally on paracrine and autocrine. Prostaglandins play an important role in physiological functions such as vasodilation (PGD2, PGE2, PGI2), gastric protection (PGI2), maintaining renal homeostasis, and platelet aggregation. Prostaglandins also play a role in mediating fever (PGE2), pain sensitivity, and inflammation (Diederich et al.)

Three isoforms of COX have been identified, namely COX-1 and COX-2. COX-1 is a glycoprotein with a molecular weight of 71kDa, which is expressed continuously (constitutively) in different tissues. COX-1 is encoded by genes on chromosome 9 and plays a role in tissue homeostasis by modulating several cellular processes ranging from cell proliferation to angiogenesis or platelet aggregation associated with thromboxane production (Kern et al.; Diederich et al.; Fujimura et al.). The difference between COX-1 and COX-2 is in the splicing, stability, and translational effectiveness of mRNA. Besides, COX-1 and COX-2 showed the ability to use different substrate sources. For example, in fibroblasts and immune cells, COX-2 can use endogenous arachidonic acid, where COX-1 cannot. In this system, COX-1 will use an exogenous substrate. 1 COX-2 is an inducible isoform of COX regulated by different growth factors and cytokines such as IL1β, IL6 or TNFα and will experience increased expression during inflammation. The COX-2 gene is present on chromosome 1. COX-2 shows 60% homology with COX-1. At the same time, COX-3 has been identified as a variant of COX-1 and is present in the brain and spine. The mechanism of action of COX-3 is not particular. Several previous studies have suggested that the COX-3 step is related to pain management, which is often associated with the movement of paracetamol (Diederich et al.).

Molecular docking is a computational method that aims to mimic the interaction event of a ligand molecule with the protein that is the target in the in-vitro test (Motiejunas and Wade). In molecular docking, the ligand molecule is attached to the active site or the mooring site of a protein at rest (static), including the co-factor and / or H2O molecules in it not. The result of docking data molecules is data regarding the position and orientation of the ligands in the active site or the mooring site. From this data, it can be concluded that the functional groups of ligands are essential for the interaction. They should not be eliminated, and the functional groups can be increased the strength of the interaction. This information guides the modification of the ligand. Given these guidelines, the conversion of ligands and the in-vitro assays of their derivatives can be carried out efficiently.

The ligand interaction with the protein above occurs only when there is a fit of shape and volume between the ligand molecule and the active site or protein binding site (Motiejunas and Wade). Besides, the functional groups on the ligand molecule must be in a good position from the amino acids paired with the active site or the mooring site (Schneider and Baringhaus).

Thus, the fit between the ligand molecule and the active site or protein anchoring site is specific, like a lock-and-key match (Motiejunas and Wade). The active site or mooring site compels (induces) changes to the ligand conformation (Foloppe and Chen; Motiejunas and Wade). With this conformational change, a certain amount of energy is released called the tethering Gibbs energy (ΔGbind) (Schneider and Baringhaus). At molecular docking, the lowest energy liberated by the ligands is considered to be the ΔGbind.

When the above match is reached, the conformation adopted by the ligand molecule is called the bioactive conformation (Schneider and Baringhaus). Meanwhile, the series of crucial functional group positions of ligands on the bioactive conformation is called pharmacophores (McInnes).

A docking simulation will be performed in this research between COX 2 with single tyramine and tyramine-Fe complexes. These analysis results are expected to provide an overview of the potential of brotowali as an anti-inflammatory for COVID-19 patients.

2. Material and Methods

The structure of the tyramine-Fe complex was drawn using the ChemDraw Pro 8.0 application. Docking was done using the AutoDock Vina 1.1 program in the Pyrx program. Docking simulations were performed between COX2-

tyramine, COX2-tyramine-Fe complexes, COX 2-aspirin, and COX 2-ibuprofen. The 3D structure of the COX 2 protein (PDB ID: 5f19) was downloaded from the RCSB database (www.rcsb.org). The structures of tyramine (PubChem ID: 5610), aspirin (PubChem ID: 2244), and ibuprofen (PubChem ID: 3672) were downloaded from the PubChem database (www.pubchem.ncbi.nlm.nih.gov). Visualization and interpretation of docking results using the Pymol v.2.3.2.1 and Discovery Studio 2019 programs.

3. Result and Discussion

Fe is a transition metal that can bind several ligands, while tyramine is an alkaloid with one –OH group (Figure 1). The metal Fe bind to the –OH group on the tyramine, forming the tyramine-Fe complex. One possibility of the complex structure is that one Fe binds to 2 tyramine molecules (Figure 2). The results showed that COX 2-tyramine binding site overlapped with COX 2-aspirin binding site (Figure 3). COX 2-tyramine interaction form hydrogen bonds on GLN203, ALA199, TYR385, and hydrophobic bonds on GLN203, ALA202. COX 2-aspirin interaction forms hydrogen bonds on TRP387, HIS386, and hydrophobic bonds on HIS388, ALA202. The energy required to form COX 2-tyramine interaction is -5.6 kcal/mol, while the energy required to form COX 2-aspirin bond is -6.4 kcal/mol (Table.1).

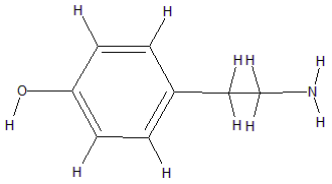

Figure 2. Single tyramine structure

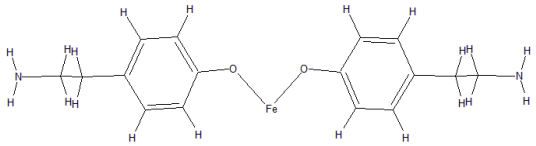

Figure 3. Structure of tyramine-Fe complex

Table 1. Binding Affinity

Interactions	Binding Affinity (kcal/mol)
COX 2-tyramine	-5.6
COX 2-aspirin	-6.4
COX 2- tyramine-Fe complex	-7.4
COX 2- ibuprofen	-6.6

The results of COX 2-tyramine-Fe complex docking as seen at the table 1. showed that COX 2-tyramine-Fe complex binding site overlapped with COX 2-ibuprofen binding site (Figure 4). COX 2-tyramine-Fe complex interaction forms hydrogen bonds on CYS41, GLN461, and hydrophobic bonds on CYS36, CYS47, PRO153, PRO156, LEU152. COX 2-ibuprofen interaction forms hydrogen bonds on ASN43 and hydrophobic bonds on LEU152, LYS468, ARG469, PRO153, CYS36, PRO40, CYS47, LEU152, PRO153, HIS39. The energy required to form COX2-tyramine-Fe bond is -7.4 kcal/mol, while the energy required to form COX 2-ibuprofen bond is -6.6 kcal/mol .

Overlaps binding sites between COX 2-tyramine with COX 2-aspirin and COX 2-complex tyramine-Fe and COX 2-ibuprofen prove that the tyramine and tyramine-Fe complexes can act as anti-inflammatory like aspirin and ibuprofen (Elhenawy et al.). However, the energy required by tyramine-Fe complex is smaller than single tyramine. The lower the energy required, the easier the bonds are to form (Kastritis and Bonvin). Tyramine-Fe complex binds more easily with COX 2 compared to single tyramine.

When interacted with COX 2, single tyramine required more energy than aspirin. However, when it has formed a tyramine-Fe complex, the energy required is smaller than ibuprofen, aspirin, and single tyramine. The number of bonds formed between COX 2 and tyramine-Fe complex was greater than that formed between COX 2 and single tyramine. Tyramine-Fe complex forms two hydrogen bonds and five hydrophobic bonds. In contrast, single tyramine forms three hydrogen bonds and two hydrophobic bonds. The greater the number of bonds, the more specific the bonds to be formed (Berg et al.). The lower energy required for bonding and the more bonds formed between COX 2-tyramine-Fe complex indicates that the tyramine-Fe complex has better anti-inflammatory activity than the single tyramine.

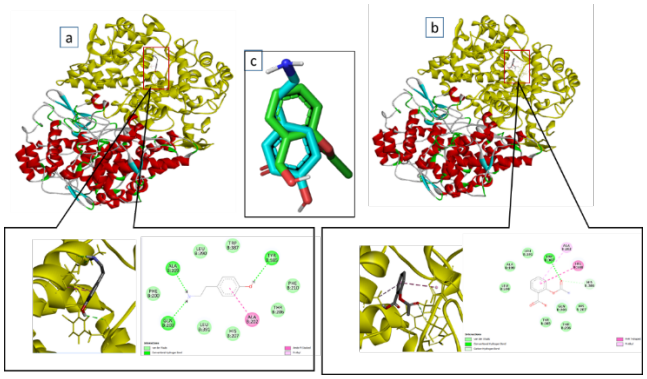

Figure 4. Comparison of docking results between COX 2-tyramine and COX 2-aspirin; (a) bond position between COX 2-tyramine, (b) bond position between and COX 2-aspirin, (C) overlap position of tyramine (blue) and aspirin (green) on COX 2.

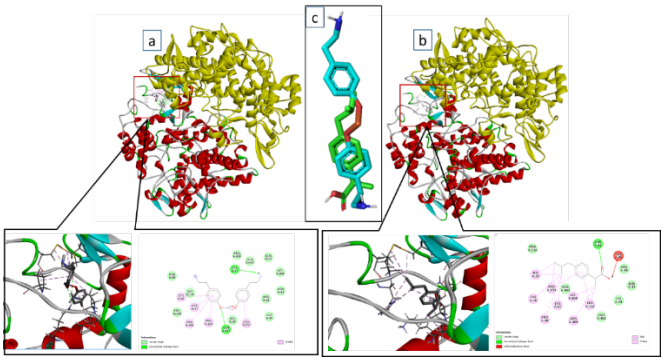

Figure 5. Comparison of docking results between COX 2-tyramine complex with Fe and COX 2-ibuprofen; (a) bond position between COX 2- tyramine complex with Fe, (b) bond position between COX2-ibuprofen, (C) overlap position between the tyramine-Fe complexes with Fe (blue) and ibuprofen (green) on COX2

Anti-inflammatory drugs such as aspirin and ibuprofen only have a single role, which is to prevent prostaglandin formation reactions (Ricciotti and Fitzgerald). Anti-inflammatory drugs also have several side effects, including gastrointestinal damage, renal syndrome, and respiratory effect (Wongrakpanich et al.). Brotowali has many compounds which have an anti-inflammatory role. Other compounds in brotowali also act as antioxidants (Ibahim et al.), immunomodulators (Abood et al.), anticholinesterases (Yusoff et al.), and antimalarials (Lee et al.). Therefore, consumption of herbal medicines, including Brotowali, is highly recommended for COVID-19.
Tyramine-Fe complex and other compounds in brotowali that have the potential as anti-inflammatory will reduce the inflammatory reaction. Besides, herbal medicine also supports and balances the system in the body so that it can eliminate infectious pathogens (Karimi et al.), including SARS-CoV-2.

4. Conclusion

Based on in silico study, the potential of anti-inflammatory activity of tyramine-Fe complex in Brotowali is better than single tyramine, aspirin and ibuprofen provide new alternative options to treat COVID-19 patient.

References

Abood, Walaa N., et al. "Immunomodulatory Effect of an Isolated Fraction from Tinospora Crispa on Intracellular Expression of INF-γ, IL-6 and IL-8." *BMC Complementary and Alternative Medicine*, 2014, doi:10.1186/1472-6882-14-205.

Ahmad, Waqas, et al. "Tinospora Crispa (L.) Hook. f. & Thomson: A Review of Its Ethnobotanical, Phytochemical, and Pharmacological Aspects." *Frontiers in Pharmacology*, vol. 7, 2016, p. 59, doi:10.3389/fphar.2016.00059.

Bebet, Nurbaeti, and Susi Mindarti. "BUKU SAKU Tanaman Obat Keluarga (TOGA)." *Isbn: 978-979-3595-49-8*, 2015.

Berg, J., et al. "Biochemistry, 5th Edition." *Biochemistry*, 2002.

Capo, Concetta R., et al. "Oleuropein Shows Copper Complexing Properties and Noxious Effect on Cultured SH-SY5Y Neuroblastoma Cells Depending on Cell Copper Content." *Journal of Trace Elements in Medicine and Biology*, 2017, doi:10.1016/j.jtemb.2017.08.002.

Chen, Linlin, et al. "Inflammatory Responses and Inflammation-Associated Diseases in Organs." *Oncotarget*, 2018, doi:10.18632/oncotarget.23208.

Dandekar, Devendra S., et al. "Cyclooxygenase-2 Inhibitor Celecoxib Augments Chemotherapeutic Drug-Induced Apoptosis by Enhancing Activation of Caspase-3 and -9 in Prostate Cancer Cells." *International Journal of Cancer*, 2005, doi:10.1002/ijc.20878.

Davis, Jennifer S., et al. "Use of Non-Steroidal Anti-Inflammatory Drugs in US Adults: Changes over Time and by Demographic." *Open Heart*, 2017, doi:10.1136/openhrt-2016-000550.

Diederich, Marc, et al. "The Role of Cyclooxygenase-2 in Cell Proliferation and Cell Death in Human Malignancies." *International Journal of Cell Biology*, 2010, doi:10.1155/2010/215158.

Dweck, Anthony C., and Cavin J. P. "Andawali (Tinospora Crispa): A Review." *Personal Care Magazine*, 2006.

Elhenawy, Ahmed A., et al. "Synthesis, Comparative Docking, and Pharmacological Activity of Naproxen Amino Acid Derivatives as Possible Anti-Inflammatory and Analgesic Agents." *Drug Design, Development and Therapy*, 2019, doi:10.2147/DDDT.S196276.

Ferrero-Miliani, L., et al. "Chronic Inflammation: Importance of NOD2 and NALP3 in Interleukin-1β Generation." *Clinical and Experimental Immunology*, 2007, doi:10.1111/j.1365-2249.2006.03261.x.

Fleit, H. B. "Chronic Inflammation." *Pathobiology of Human Disease: A Dynamic Encyclopedia of Disease Mechanisms*, 2014, doi:10.1016/B978-0-12-386456-7.01808-6.

Foloppe, Nicolas, and I. Jen Chen. "Conformational Sampling and Energetics of Drug-Like Molecules." *Current Medicinal Chemistry*, 2009, doi:10.2174/092986709789057680.

Fujimura, Takashi, et al. "Role of Cyclooxygenase-2 in the Carcinogenesis of Gastrointestinal Tract Cancers: A Review and Report of Personal Experience." *World Journal of Gastroenterology*, 2006, doi:10.3748/wjg.v12.i9.1336.

Guan, W., et al. "Clinical Characteristics of Coronavirus Disease 2019 in China." *New England Journal of Medicine*, 2020, doi:10.1056/NEJMoa2002032.

Hipol, Regina Lourdes B., et al. "Anti-Inflammatory Activities of the Aqueous Extract of the Stem of Tinospora Crispa (Family Menispermaceae)." *Journal of Nature Studies*, 2012.

Ibahim, M. J., et al. "Anti-Proliperative and Antioxidant Effects of Tinospora Crispa (Batawali)." *Biomedical Research*, 2011.

Kamarazaman, Ihsan Safwan, et al. "Inhibitory Properties of Tinospora Crispa Extracts on TNF-α Induced Inflammation on Human Umbilical Vein Endothelial Cells (HUVECS)." *International Journal of Tropical Medicine*, 2012, doi:10.3923/ijtmed.2012.24.29.

Karimi, Ali, et al. "Herbal versus Synthetic Drugs; Beliefs and Facts." *Journal of Nephropharmacology*, 2015.

Kastritis, Panagiotis L., and Alexandre M. J. J. Bonvin. "On the Binding Affinity of Macromolecular Interactions: Daring to Ask Why Proteins Interact." *Journal of the Royal Society Interface*, 2013, doi:10.1098/rsif.2012.0835.

Kern, Michael A., et al. "Cyclooxygenase-2 Inhibition Induces Apoptosis Signaling via Death Receptors and Mitochondria in Hepatocellular Carcinoma." *Cancer Research*, 2006, doi:10.1158/0008-5472.CAN-06-0325.

Lee, WeiCai, et al. "In Vivo Antimalarial Potential of Tinospora Crispa Miers in Mice and Identification of the

Bioactive Compound." *Pharmacognosy Magazine*, 2020, doi:10.4103/pm.pm_10_19.
McInnes, Campbell. "Virtual Screening Strategies in Drug Discovery." *Current Opinion in Chemical Biology*, 2007, doi:10.1016/j.cbpa.2007.08.033.
Motiejunas, D., and R. C. Wade. "Structural, Energetic, and Dynamic Aspects of Ligand-Receptor Interactions." *Comprehensive Medicinal Chemistry II*, 2006, doi:10.1016/b0-08-045044-x/00250-9.
Pathak, Ashish K., et al. "Chemistry and Biological Activities of the Genera Tinospora." *Pharmaceutical Biology*, 1995, doi:10.3109/13880209509065379.
Praman, Siwaporn, et al. "Hypotensive and Cardio-Chronotropic Constituents of Tinospora Crispa and Mechanisms of Action on the Cardiovascular System in Anesthetized Rats." *Journal of Ethnopharmacology*, 2012, doi:10.1016/j.jep.2012.01.006.
Quisumbing, Eduardo. "Medicinal Plants of the Philippines." *Tech. Bull.*, 1951.
Rahman, Nik Najib Nik A., et al. "Antimalarial Activity of Extracts of Malaysian Medicinal Plants." *Journal of Ethnopharmacology*, 1999, doi:10.1016/S0378-8741(98)00135-4.
Ricciotti, Emanuela, and Garret A. Fitzgerald. "Prostaglandins and Inflammation." *Arteriosclerosis, Thrombosis, and Vascular Biology*, 2011, doi:10.1161/ATVBAHA.110.207449.
Rungruang, Thanaporn, and Thidarut Boonmars. "In Vivo Antiparasitic Activity of the Thai Traditional Medicine Plant-Tinospora Crispa-against Plasmodium Yoelii." *Southeast Asian Journal of Tropical Medicine and Public Health*, 2009.
Schneider, Gisbert, and Karl-Heinz Baringhaus. "Molecular Design. Concepts and Applications." *RECIIS*, 2008.
Shang, Jian, et al. "Structural Basis of Receptor Recognition by SARS-CoV-2." *Nature*, 2020, doi:10.1038/s41586-020-2179-y.
Sharma, Priyanka, et al. "The Chemical Constituents and Diverse Pharmacological Importance of Tinospora Cordifolia." *Heliyon*, 2019, doi:10.1016/j.heliyon.2019.e02437.
Souto, Augusto Lopes, et al. "Anti-Inflammatory Activity of Alkaloids: An Update from 2000 to 2010." *Molecules*, 2011, doi:10.3390/molecules16108515.
Sukmaningsih, A. A. S. A., et al. "Investigating Natural Transition Metal Coordination Anthocyanin Complex in Java Plum (Syzygium Cumini) Fruit as Free Radical Scavenging." *Rasayan Journal of Chemistry*, 2018, doi:10.31788/RJC.2018.1133047.
Wongrakpanich, Supakanya, et al. "A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in the Elderly." *Aging and Disease*, 2018, doi:10.14336/AD.2017.0306.
Youdim, Moussa B. H. *Monoamine Oxidases and Their Inhibitors BT - Encyclopedia of Molecular Pharmacology*. Edited by Stefan Offermanns and Walter Rosenthal, Springer Berlin Heidelberg, 2008, pp. 783–91, doi:10.1007/978-3-540-38918-7_191.
Yusoff, Mashitah, et al. "Anticholinesterase Inhibitory Activity of Quaternary Alkaloids from Tinospora Crispa." *Molecules*, 2014, doi:10.3390/molecules19011201.
Zarghi, Afshin, and Sara Arfaei. "Selective COX-2 Inhibitors: A Review of Their Structure-Activity Relationships." *Iranian Journal of Pharmaceutical Research*, 2011, doi:10.22037/ijpr.2011.1047.

Biography

Wimbuh Tri Widodo is a doctoral student from Brawijaya University. He has a Bachelor of Biological Sciences from Jember University. He has published journal and conference papers. Mr Wimbuh Tri Widodo is a lecturer and researcher at STIKes Karya Putra Bangsa Tulungagung His research interests, Biology Molecular, Parasitology, Microbiology

Sri Widyarti is an Associate Professor, She has a Bachelor of Biological Sciences from Airlangga University, a Master's degree from Institute Pertanian Bogor, and Ph.D. from Brawijaya University. She has published journal and conference papers. Mrs. Widyarti is a lecturer and researcher at the Biological Department, Faculty of Mathematics and Natural Sciences, Brawijaya University. Her research interests Cell biology, molecular and cellular biology, immunology, molecular analysis techniques.

DJ Djoko Herry Santjojois an Associate Professor, He has published journal and conference papers. Mr. Djoko is a lecturer and researcher at the Physics Department, Faculty of Mathematics and Natural Sciences, Brawijaya University. Her research interests Material physics, quantum physics

Sutiman Bambang Sumitro is a Professor, He has a Bachelor of Biological Sciences from Gadjah Mada University, a Master's degree from Gadjah Mada University, and Ph.D. from Graduate School of Biology, Nagoya University. He has published journal and conference papers. Mr. Sutiman is a lecturer and researcher at the Biological Department, Faculty of Mathematics and Natural Sciences, Brawijaya University, Malang. His research interests Cell biology, molecular and cellular Biology, Nano Biology, microscopic observation techniques.