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Literature Review : Study of Molecular Mechanism Level of NSAID Class Of Drugs As COX-2 Inhibitors

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ABSTRACT

NSAIDs (Non-Steroid Anti-Inflammatory Drugs) are drugs that can treat pain and inflammation. The therapeutic effect of NSAIDs as anti-inflammatory analgesics is that they have the ability to inhibit the biosynthesis of prostaglandins which are pain mediators. This prostaglandin has a major role in inhibiting the COX enzyme (cyclooxygenase) in which COX has two isoforms, namely COX1 isoenzyme (non-selective) and COX2 isoenzyme (selective). Tricyclic COX-2 selective inhibitors work by blocking COX-2. COX-2 binds to PD-L1 via the PGE2 pathway and affects macrophages in suppressing myeloid. COX-2 has functions including producing reactive oxygen species that are responsible for DNA damage, activating substances that deviate from intracellular pathways such as the MAPK and PI3 K/AKT pathways, activating STAT3, inducing Bcl-2, and producing growth factors including growth factors. epidermal (EGF)) and fibroblast growth factor (FGF).

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1. INTRODUCTION

Inflammation is a response of the body to the presence of tissue damage or natural tissue manifestations. Inflammation results in the accumulation of white blood cells, especially neutrophils and monocytes to eliminate or limit the causative agent. Neutrophils will perform margination, chemotosis, emigration and phagocytosis [1].

Inflammation is also a physiological response in the form of resistance to the environment around the body due to injury to repair damaged tissue and destroy the causative agents of the inflammation. Drugs that are often used to treat analgesics and anti-inflammatories are NSAIDs (Non Steroidal Anti-inflammatory Drugs). The therapeutic effect of NSAIDs as an analgesic anti-inflammatory, comes from the ability to be able to inhibit the biosynthesis of prostaglandins that are pain mediators. This prostaglandin has the main function in inhibition of the COX enzyme (cyclooxygenase) where COX has two isoforms, namely the COX1 isoenzyme (non-selective) and the COX2 isoenzyme (selective) [2].

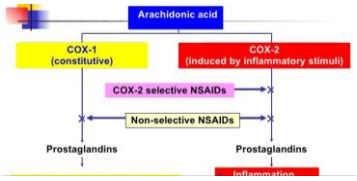

Figure 1. Cyclooxygenase Enzyme Group

Arachidonic acid is one of the important inflammatory mediators, arachidonic acid plays a role in the biosynthesis of prostaglandins through the cyclooxygenase pathway.2 Cyclooxygenase-1 (COX-1) plays a role in normal physiological functions such as mucus secretion to protect the digestive mucosa and to maintain kidney function. Cyclooxygenase-2 (COX-2) is an enzyme whose existence is influenced by stimuli in tissues. Such stimuli can be cytokines, bacterial lipopolysaccharides, inflammatory or other pathological states [1].

Cyclooxygenase (COX-1 and COX-2) catalyzes rate-limiting steps in the biosynthesis of prostaglandins, prostacyclines, and thromboxane. These powerful lipid signaling molecules regulate the "housekeeping" function necessary for normal physiological activity. OX-mediated changes in prostaglandin production are associated with a variety of disease pathologies, including inflammation, cardiovascular disease, and cancer. COX-1 and COX-2 are bifunctional enzymes that perform two sequential reactions at spatially different but mechanically combined active sites. COX-1 and COX-2 are pharmacological targets of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective inhibitors of COX-2 (coxib). These compounds are some of the most widely used drugs in the world, used to reduce acute and chronic inflammation and protect against adverse cardiovascular events [2].

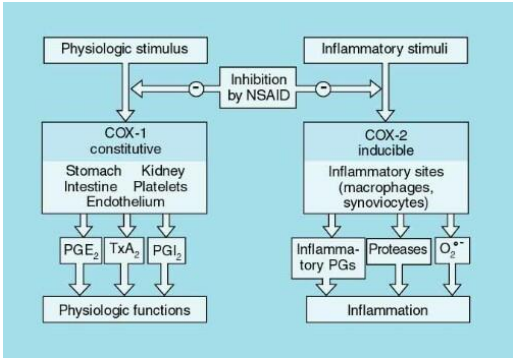

Figure 2. Working Mechanism of COX1 and COX2

Previously it was known that the COX enzyme is of two types, one prevailing at the site of inflammation (COX-2) and the other occurring most in the gastrointestinal tract (COX-1). This discovery demonstrates the important role of the progress of healing COX-2 inhibitors. So NSAID drugs can help to treat inflammation [3].

2. METHOD

In the journal review conducted using the literature study method with the collection of journals that will be reviewed. The journals used are from Google Scholar and PubMed with the search method using the keywords "COX 2 NSAID", "COX2 inhibitor", "COX 2 Inhibitor NSAID Drugs" between 2012-2022. The results obtained were 33 journals and only 15 relevant journals, then the journals were screened and reviewed in each journal.

3. RESULTS AND DISCUSSION

Table 1. Article Review

References	Method	Substance	Drug Class	Pharmacology Mechanism
(Soleha et al., 2018)	Questionnaire Analysis	Colecoxib	NSAID (Selective)	Selective inhibition of COX-2 enzyme activity, so

				that the conversion process of arachidonic acid to prostaglandins is disrupted
(Eko, 2012)	Literature Study	Rofecoxib	NSAID (Selective)	Selective inhibition of COX-2 enzyme activity, so that prostaglandins biosynthesis inhibited
(Kresnadi & Mulyo, 2016)	Quasi Experiment	Etoricoxib	NSAID (Selective)	Selective inhibition of COX-2 enzyme activity, so that the conversion of arachidonic acid to PPG2 is disrupted
(Bare, 2022)	Molecular Docking	Phloroglucinol	Synthetic compound	Phloroglucinol binds to COX-2 protein resulting in a protein-ligand complex forming amino acid residues SER143, in domain A. In LEU224, GLY225, THR237, GLY235 in domain B. This binding is supported by van der Waals forces LEU145, HIS226, ASN375, PHE142, GLU236 , ASP239, TYR234, GLN241, LYS333, GLU140, GLN330, SER146, ASN144, and LEU145. Phloroglucinol binds specifically to COX-2, inhibits the activation of prostacyclin (PGI2), thereby stopping the stimulus of prostaglandin G2 into prostaglandin H2 which can reduce inflammation in the body.
(Desai et al., 2018)	Literature Study	Genistein	Isoflavonoid Compound	Genistein inhibits cell proliferation and induces apoptosis. Genistein also inhibits hepatocellular carcinoma cell migration by reversing the epithelial-mesenchymal transition and suppressing COX-2

				expression. Genistein suppresses the production of COX-2 and NFk protein levels so that DNA B binding activity is reduced. Genistein inhibits TPA-induced COX-2 expression and NF-kB transcriptional activity in MCF10A human breast epithelial cells by blocking ERK-mediated p65/RelA phosphorylation in human breast epithelial cells thereby inhibiting COX-2 expression in MCF-7 breast cancer cells.
(Sadeq, 2018)	Piroxicam . Induced Knee Joint Pain Patient Data Collection	Piroxicam	NSAID (Non-Selective)	With the inhibition of the COX-1/2 enzyme, the process of inversion of arachidonic acid into prostaglandins is disrupted.
(Hidayat, 2020)	Literatur Study	Paracetamol	Antipyretic Analgesic (Not NSAID)	Inhibits the secondary peroxidase step involved in the synthesis of prostanoids by cyclooxygenase enzymes (COX-1 and COX-2). Paracetamol can act as a reducing agent for PGG2 and heme cosubstrates that inhibit the POX catalytic process by converting the heme group to an inactive reduced state.
(Widjaja et al., 2013)	TLC-Spectrophotodensitometry Identification	Indometasin	NSAID (Non-Selective)	Inhibits prostaglandin synthesis by inhibition of COX-1 and COX-2 . enzymes
(Chen & Ouyang, 2017))	Molecular Docking	Ketoprofen	NSAID (Non-Selective)	Inhibits two isoforms of cyclooxygenase (COX), namely COX1 and COX-2 from forming prostaglandins through the arachidonic acid pathway.

(Dinata et al., 2014)	Molecular docking simulation	Xantorhizol	Has anti-inflammatory activity	Xanthorrhizol compounds can bind to binding pocket for COX-1 and COX-2 enzymes, but more selective for the COX-2 enzyme with a lower docking energy value than its interaction with the COX-1 enzyme.
(Orlando et al., 2015)	Crystallization and Data Collection	Ibuprofen	NSAID (Non-Selective)	Substrate selective inhibition by binding of one COX-2 dimer monomer inhibits allosteric endocannabinoid
(Kumar Vishwakarma & Negi, 2020)	Reviewing articles	Aspirin	NSAID (Non-Selective)	Inhibits COX enzyme activity thereby inhibiting the biosynthesis of prostaglandin E2 (PGE2) and thromboxane A2 and has a duration of action of 4-6 hours.
(Ruslin et al., 2022)	Molecular Docking	Naproxen	NSAIDs (COX-2 Selective)	Making a pharmacophore model using ZINC ligand. Pharmacophores greatly affect the inhibition of cox-2 activity. A total of 1675 molecules were tethered to the COX-2 enzyme to predict its binding mode and affinity. The complex is able to bind to the COX-2 active site.
(Ayoub, 2021)	Literature Study	Paracetamol	Antipyretic Analgesic (Non NSAID)	Paracetamol inhibits the COX-1 and COX-2 enzymes in PGE2. This inhibition comes from the brain and prostaglandins from the spinal cord. The inhibitory activity of COX-1 and COX-2 enzymes by paracetamol was weak. The inhibitory selectivity of COX-3 over COX-1 and COX-2, which is dependent on the substrate arachidonic acid

				concentration indicating blockage at the active site
Adiansyah Evani EPS, et al (2021)	Literature Study	Naproxen	NSAID (Non-Selective)	Blocking arachidonic binding competitively inhibits the cyclooxygenase (COX) isoenzymes, COX1 and COX2, resulting in analgesic and anti-inflammatory effects.

COX-2 is a potential target as an antitumor with chemotherapy and radiotherapy mechanisms. The molecular targets are proliferation-related molecules such as VEGFR or aromatase inhibitors. COX-2 which binds to PD-L1 has an effect on breast cancer cells. COX-2 binds to PD-L1 via the PGE2 pathway and affects macrophages in suppressing myeloid. COX-2 has functions including producing reactive oxygen species that are responsible for DNA damage, activating substances that deviate from intracellular pathways such as the MAPK and PI3 K/AKT pathways, activating STAT3, inducing Bcl-2, and producing growth factors including growth factors. epidermal (EGF)) and fibroblast growth factor (FGF). COX-2 is involved in the proliferation of melanoma cells with or without BRAF/NRAS mutations with the COX-2 inhibitor celecoxib inhibiting their proliferation and inducing cell death. In cell line A375 inhibition of cell proliferation or induction of cell death by celecoxib was associated with NF-B-mediated down-regulation of Bcl-2. The binding of SK-MEL-2 with celecoxib did not make Bcl-2 expressed. COX-2 has been implicated in suppressing the activity of immune cells such as dendritic cells, natural killers and T cells as well as in promoting type-2 immunity leading to tumor immune evasion [19].

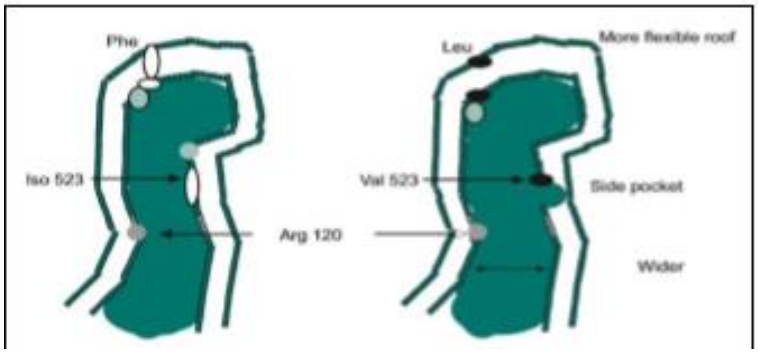

Figure 3. Morphology Of Cox-1 (Left) And Cox2 (Right) Enzyme

Tricyclic COX-2 selective inhibitors work by blocking COX-2. The selectivity was achieved due to the weight measure of the tricyclic inhibitor C0X-2. There is leucine in COX-2 in place of phenylalanine in COX-1, which shows greater flexibility on the up side of the active site in COX-2. NSAIDs bind to COX-1 by reversible hydrogen bonding and inhibition by simple steric inhibition, leading to a large variation between COX-1 and COX-2, and in this way, selectivity can be achieved. COX-2 inhibitors are time-dependent active processes by blocking lower enzyme sites. The presence of COX-2 mostly in the perinuclear sheath and COX-1 in the perinuclear membrane and endoplasmic reticulum released by different PLA2 enzymes varied for each COX. COX-2 shows low hydroperoxide level while COX-1 shows high hydroperoxide level. Three enzymes catalyze the formation of PGE2 from PGH2 namely membrane bound PGES (mPGES)-1, mPGES-2, and cytosolic PGES (cPGES). The inhibitory activity of COX-2 makes an ideal NSAID therapy, whereas inhibition of COX-1 causes

problems such as gastric ulcers and decreased platelet aggregation. COX-2 induction affects the increase in production. G. PGE acts on peripheral sensory nerve endings in inflammatory media so that it is widely applied as a COX product for the transmission of pain responses through the spinal cord.

COX-2 inhibitors can inhibit hyperalgesia in mice. In humans, selective COX-2 inhibitors such as rofecoxib exhibit analgesic effects when used after dental surgery. COX-2 has been recognized in esophageal, gastric, and pancreatic cancer. The effect of NSAIDs related to COX suppressive activity is to reduce the risk of developing Alzheimer's disease and reduce inflammation. COX-2 is elevated in the frontal cortex of the brain in cases of Alzheimer's disease. PPAR-γ receptors and both COX-induced isoforms are also elevated in the temporal cortex of the brain in Alzheimer's cases because COX-2 is stimulated in neurons after kainic acid-induced seizures that are susceptible to apoptosis (14].

The COX isoform is a homodimer consisting of a signal peptide, an epidermal growth factor (EGF) domain, a membrane-binding domain, and a large C-terminal catalytic domain. The catalytic domain constitutes the majority of COX monomers and acts as a site for substrate binding and NSAID action. The catalytic domain contains two different enzyme active sites, namely the cyclooxygenase and peroxidase active sites. The peroxidase active site is found at the interface between the large and small lobes of the catalytic domain. Peroxidase activity is not affected by cyclooxygenase activity whereas cyclooxygenase requires a group at the peroxidase site to undergo two-electron oxidation. The cyclooxygenase active site is a long, narrow, predominantly hydrophobic blind channel that extends from the base of the membrane-binding domain through helices A, B, and C to the center of the catalytic domain on the opposite side of the peroxidase active site. The presence of a side pocket in COX-2 located above the Arg120/Tyr355/Glu524 constriction is the only difference between the COX-1 and COX-2 active sites [20].

PTUPB or trifluoromethylphenyl-ureido-propyl-pyrazole-1-yl-benzenasulfonamide can block TGF-βAECs that arise due to interference with TGF-β pathway 1-Smad2/3 induced by AECs. PTUTB can also inhibit the synthesis of TGF-βMEA. PTUPB can block EMT AEC by upregulating Nrf2 and inhibiting the TGF-β signaling pathway 1-Smad2/3. Arachidonic acid (ARA) is one of the most abundant polyunsaturated fatty acids in the body. Inhibition of sEH (Soluble epoxide hydrolase) can increase the content of endogenous EET (Epoxyeicosatrienoic acids) and reduce the EMT (Epithelial-mesenchymal transition) process. However, ARA on other lines promotes EMT. The expression of sEH and COX-2 proteins was significantly increased during TGF-β1-induced EMT processes, manifested by impaired CYP/COX-2 metabolism in ARA. PTUPB is a COX-2 and sEH inhibitor. ROS is an important signal for EMT initiation. It has been found that restoring intracellular antioxidant signaling pathways can reduce TGF-β1-induced EMT. For example, piperine enhances the Nrf2 antioxidant cascade, reduces TGF-β1-induced ROS accumulation, and eliminates EMT in AML-12 hepatocytes. TGF-βSmads 1-activated plays an important role in the EMT process. The combination of transcriptionally activated Smad2 or Smad3 and Smad4 can regulate EMT, expression of Smad2 or Smad3 can reduce TGF-β1-induced EMT. TGF-β1 activates TβRI by acting on the receptor complex and directly phosphorylating the C-terminal Smad2 and Smad3. After phosphorylation, Smad2, Smad3, and Smad4 form trimers, which are transported to the nucleus, bind to DNA-binding transcription factors, and cooperatively regulate transcription of target genes [21].

Macrophage cells increase the production of proinflammatory molecules after exposure to stimulators such as LPS and LTA through their surface receptors, namely Toll-like receptors TLR4 and TLR2. Rutaecarpine's antiplatelet mechanism is via suppression of phosphoinositide 3-kinase (PI3K)/Akt/MAPK, p38-mediated activation of NF-B, and the PI3K/Akt/glycogen synthase kinase-3β (GSK3β) signaling cascade. Rutaecarpine inhibits inflammatory molecules such as NO, iNOS, COX-2, and IL-1β expression in LTA, a component of the cell wall of Gram-positive bacteria, which induces RAW cells. NO plays a role in the pathogenesis of several inflammatory disorders, and its production in activated macrophages via iNOS induces several acute and chronic inflammatory conditions. Overexpression of iNOS and COX-2 stimulates NO and PGE2 activation in activated macrophages, respectively, leading to chronic inflammation. The inflammatory process strongly induces the

expression of iNOS and COX-2, which increase NO and prostaglandin E2 (PGE2) products, respectively. IL-1β stimulated by endotoxin. Rut has the ability to inhibit TLR2 and TLR4 receptor-mediated inflammatory markers. MAPK signaling pathways, including ERK, JNK, and p38, participate in the production of various neuroinflammatory mediators. ERK is triggered by MAP kinase kinase (MKK) and MKK2, JNK by MKK4 and MKK7, and p38 MAP kinase by MKK3, MKK4, and MKK6. The p38 MAPK trigger has been established to be associated with LTA-induced COX-2 expression and PGE2 release in human lung epithelial cells. A previous study has also shown that p38 MAPK activation involves LPS-induced iNOS expression and NO release in RAW cells. LTA-treated RAW cells also induced significant p38 MAPK activation. SB 203580, a p38 MAPK inhibitor, inhibits LTA-induced iNOS expression and NO release. ERK and JNK activation is essential for NO production. ERK and JNK inhibitors expressively decrease iNOS expression and NO production in microglial culture. ERK and JNK are immediately phosphorylated upon LTA exposure. Rutaecarpine induces an anti-inflammatory effect on LTA-stimulated RAW cells, in part through inhibition of p38 MAPK and ERK activation. NF-kB plays an important role in NO production in LPS-activated microglia, which is achieved relatively through activation of the MAPK signaling pathway. In normal cells, nuclear factor inhibitor B-α (IκBα) controls NF-B by binding to and inactivating the transcriptional activity of NF-B in the cytoplasm. Upon stimulation, inhibitory core factor B kinase activates which phosphorylate IκBα and result in IκBα degradation, consequently releasing the NF-κB p50/p65 heterodimer to enter the nucleus. Activating NF-kB and demonstrating a dynamic role in the anti-inflammatory effect of Rutaecarpine, lucyoside B attracts NF-B transcriptional activity, which is associated with decreased IκBα phosphorylation, degradation, and translocation of p65. Rutaecarpine inhibits NF-B activation and reduces the toxin-induced inflammatory response of Gram-positive bacteria [22].

4. CONCLUSION

NSAIDs (*Non Steroidal Anti-inflammatory Drugs)* are analgetic anti-inflammatory drugs that can inhibit prostaglandin biosynthesis. Prostaglandins serve for inhibition of the COX enzyme (cyclooxygenase) where COX has two isoforms, namely the COX1 isoenzyme (non-selective) and the COX2 isoenzyme (selective). Drugs that can inhibit the COX 1 and COX 2 enzymes include Celecoxib, Rofecoxib, Etoricoxib, Phloroglucinol, Genistein, Piroxicam, Paracetamol, Indomethacin, Ketoprofen, Xantorhizol, Ibuprofen, Aspirin, and Naproxen. The effect of NSAIDs associated with COX suppression activity is to reduce the danger of developing Alzheimer's disease and reduce inflammation.

REFERENCES

[1] E. Kusumastuti, J. Handajani, and Heni Susilowati, "Ekspresi COX-2 dan Jumlah Neutrofil Fase Inflamasi pada Proses Penyembuhan Luka Setelah Pemberian Sistemik Ekstrak Etanolik Rosela (Hibiscus sabdariffa) (studi in vivo pada Tikus Wistar)," Majalah Kedokteran Gigi Indonesia, vol. 21, no. 1, pp. 13–19, 2014.

[2] Y. Aulia, F. Safitri, and R. Fadilah, "EFEK ANTI INFLAMASI EKSTRAK ETANOL WORTEL (DAUCUS CAROTA L.) TERHADAP TIKUS STRAIN WISTAR (RATTUS NOVERGICUS) YANG DIINJEKSI KARAGENAN," Saintika Medika: Jurnal Ilmu Kesehaan dan Kedokteran Keluarga, vol. 9, no. 2, pp. 65–69, 2013.

[3] M. Soleha, A. Isnawati, N. Fitri, R. Adelina, H. T. Soblia, and W. Winarsih, "Profil Penggunaan Obat Antiinflamasi Nonstreoid di Indonesia," *Jurnal Kefarmasian Indonesia*, pp. 109–117, Oct. 2018, doi: 10.22435/jki.v8i2.316.

[4] T. Eko, "PENGGUNAAN COXIB DALAM TATA LAKSANA NYERI NOSISEPTIF," *Medicina Jurnal Ilmiah Kedokteran*, vol. 43, no. 1, pp. 23–30, 2012.

[5] D. Kresnadi and K. Mulyo, "PERBANDINGAN PENGARUH PEMBERIAN ANALGETIK COX-2 DENGAN ASAM MEFENAMAT TERHADAP RASA NYERI PASCA ODONTEKTOMI (IMPAKSI KELAS 1, MOLAR 3 RAHANG BAWAH)," 2016.

[6] Y. Bare, "Interaction Phloroglucinol as inflammation therapy through Cyclooxygenase-2 (COX-2) gene inhibition," *Jurnal Ilmiah Medicamento*, vol. 8, no. 1, pp. 14–21, Mar. 2022, doi: 10.36733/medicamento.v8i1.3162.

[7] S. J. Desai, B. Prickril, and A. Rasooly, "Mechanisms of Phytonutrient Modulation of Cyclooxygenase-2 (COX-2) and Inflammation Related to Cancer," *Nutrition and Cancer*, vol. 70, no. 3. Routledge, pp. 350–375, Apr. 03, 2018. doi: 10.1080/01635581.2018.1446091.

[8] O. R. Sadeq, "The effects of mini-dose aspirin on hepatic functions. View project," 2018. [Online]. Available: https://www.researchgate.net/publication/324418484

[9] R. P. Hidayat, "N-ACETYLCYSTEINE SEBAGAI TERAPI TOKSISITAS ACETAMINOPHEN," *Jurnal Medika Hutama*, vol. 2, no. 1, pp. 231–237, 2020, [Online]. Available: http://jurnalmedikahutama.com

[10] I. N. Widjaja, K. Cahyadi, A. Wahyudhie, and I. MAG Wirasuta, "Pengembangan Metode Identifikasi Indometasin dengan KLT-Spektrofotodensitometri," *Jurnal Farmasi Udayana*, vol. 2, no. 1, pp. 17–24, 2013.

[11] W. Chen and D. Ouyang, "Investigation of molecular dissolution mechanism of ketoprofen binary and ternary solid dispersions by molecular dynamics simulations," *Mol Simul*, vol. 43, no. 13–16, pp. 1074–1080, 2017, doi: 10.1080/08927022.2017.1321755.

[12] D. I. Dinata, H. Suryatno, I. Musfiroh, and S. E. Suherman, "Simulasi Docking Molekuler Senyawa Xanthorrhizol sebagai Antiinflamasi terhadap Enzim COX-1 dan COX-2," *Indonesian Journal of Pharmaceutical Science and Technology*, vol. 1, no. 1, pp. 7–13, 2014, [Online]. Available: www.pdb.com.

[13] B. J. Orlando, M. J. Lucido, and M. G. Malkowski, "The structure of ibuprofen bound to cyclooxygenase-2," *J Struct Biol*, vol. 189, no. 1, pp. 62–66, Jan. 2015, doi: 10.1016/j.jsb.2014.11.005.

[14] R. Kumar Vishwakarma and D. S. Negi, "THE DEVELOPMENT OF COX-1 AND COX-2 INHIBITORS: A REVIEW," *Int J Pharm Sci Res*, vol. 11, no. 8, p. 3544, 2020, doi: 10.13040/IJPSR.0975-8232.11(8).3544-55.

[15] R. Ruslin *et al.*, "The Search for Cyclooxygenase-2 (COX-2) Inhibitors for the Treatment of Inflammation Disease: An in-silico Study," *J Multidiscip Healthc*, vol. 15, pp. 783–791, 2022, doi: 10.2147/JMDH.S359429.

[16] S. S. Ayoub, "Paracetamol (acetaminophen): A familiar drug with an unexplained mechanism of action," *Temperature*, vol. 8, no. 4, pp. 1–22, 2021, doi: 10.1080/23328940.2021.1886392.

[17] E. E. P. S. Adiansyah, H. Ariyani, and Hendera, "STUDI LITERATUR EFEK PENGGUNAAN NON-STEROIDAL ANTI INFLAMMATORY DRUGS (NSAID) PADA SISTEM GASTROINTESTINAL (Literature Study Of The Non-Steroidal Anti Inflammatory Drugs (NSAIDs) On The Gastrointestinal System)," *Journal of Current Pharmaceutical Sciences*, vol. 5, no. 1, pp. 418–428, 2021.

[18] G. Botti *et al.*, "COX-2 expression positively correlates with PD-L1 expression in human melanoma cells," *J Transl Med*, vol. 15, no. 1, pp. 1–12, Feb. 2017, doi: 10.1186/s12967-017- 1150-7.

[19] R. Kumar Vishwakarma and D. S. Negi, "THE DEVELOPMENT OF COX-1 AND COX-2 INHIBITORS: A REVIEW," *Int J Pharm Sci Res*, vol. 11, no. 8, p. 3544, 2020, doi: 10.13040/IJPSR.0975-8232.11(8).3544-55.

[20] J. J. P, S. L. Manju, K. R. Ethiraj, and G. Elias, "Safer anti-inflammatory therapy through dual COX-2/5-LOX inhibitors: A structure-based approach," *European Journal of Pharmaceutical Sciences*, vol. 121. Elsevier B.V., pp. 356–381, Aug. 30, 2018. doi: 10.1016/j.ejps.2018.06.003.

[21] C. Y. Zhang *et al.*, "COX-2/sEH Dual Inhibitor PTUPB Attenuates Epithelial-Mesenchymal Transformation of Alveolar Epithelial Cells via Nrf2-Mediated Inhibition of TGF- β 1/Smad Signaling," *Oxid Med Cell Longev*, vol. 2022, 2022, doi: 10.1155/2022/5759626.

[22] T. Jayakumar *et al.*, "Anti-Inflammatory Mechanism of An Alkaloid Rutaecarpine in LTA-Stimulated RAW 264.7 Cells: Pivotal Role on NF-κB and ERK/p38 Signaling Molecules," *Int J Mol Sci*, vol. 23, no. 11, Jun. 2022, doi: 10.3390/ijms23115889.