IN-SILICO COMPARISON OF DRUGS AND NATURAL COMPOUNDS TOWARDS INFLAMMATION DISEASE

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Abstract

The study on the inhibition of Interleukin-1, Cyclooxygenase-2, Toll-like receptor 4, and Human Phospholipase A2 was an important approach for inflammation treatment. The inhibition of the protein target of inflammation, Interleukin-1, Cyclooxygenase-2, Toll-like receptor 4, and Human Phospholipase A2 using synthetic and natural inhibitors were studied. Synthetic compounds Ibuprofen, Flurbiprofen, and Indomethacin and natural compounds such as Curcumin, Gallic acid, Artemisinin, Rosmarinic acid, and Andrographolide was used in this study. The purpose of this research is to identify the potential inhibitor of natural compound as anti-inflammation towards Interleukin-1, Cyclooxygenase-2, Toll-like receptor 4, and Human Phospholipase A2. In this research, molecular docking methods were used to identify the compound that has the best interaction energy towards the Interleukin-1, Cyclooxygenase-2, Toll-like receptor 4, and Human Phospholipase A2 protein targets. In structure-based drug design, molecular docking method is used because of their ability to predict the binding-conformation of small-molecule ligands to the target binding site as the main objective of molecular docking is to attain a ligand-receptor complex with optimized conformation and with the intention of processing less binding free energy. The results obtained from the docking using Autodock Vina software showed that the best affinity binding was observed. The molecular interactions were then further analyzed using Discovery Studio Visualizer. Based on the molecular docking studies, Andrographolide, Artemisinin, Rosmarinic Acid and Curcumin was chosen as the potential inhibitor chosen for 5UCA, 2NRU, 3PGH for anti-inflammatory. It is hoped that this study can create new discoveries in an effort to find potential inhibitors for inflammatory disease.

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1.Backgroud of Study

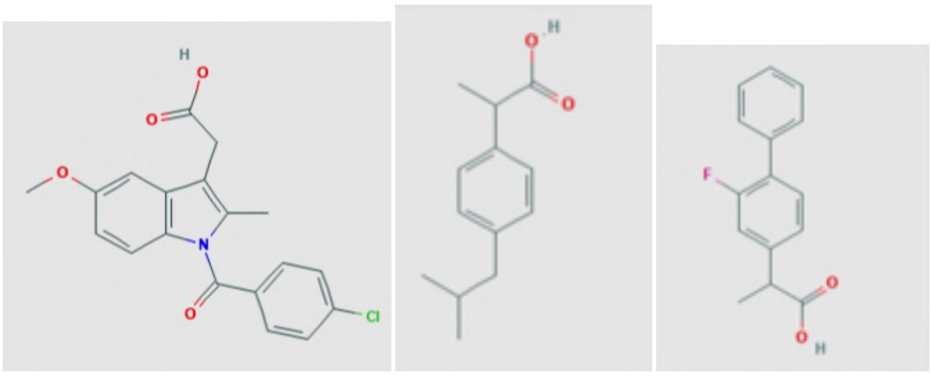
1.1 Literature

Inflammation is the mechanism by which the immune system body, such as white blood cells, and the objects they produce, shield you from infection by foreign invaders, such as bacteria and viruses. However, in certain conditions, like arthritis, the protection mechanism of the body causes inflammation because there are no invaders to fend off. The immune system behaves as if the tissues are compromised or otherwise unusual in these autoimmune diseases, causing damage. Acute inflammation and chronic inflammation are two forms of inflammation. Depending on the source, acute inflammation typically occurs within hours or days. They will quickly become serious in some situations. How inflammation develops and how long they last will depend on the cause, which part of the body they affect, and individual factors [1]. Chronic inflammation usually lasts within months or years, or even after the first trigger is gone. The conditions associated with chronic inflammation are cancer, diabetes, asthma, heart disease and Alzheimer's disease. Non-steroidal anti-inflammatory medications (NSAIDs) and hormones are extensively used to treat inflammatory responses [2]. The integration of silicone techniques facilitates the search for novel anti-inflammatory medicinal products with improved pharmacokinetic and toxicological profiles than currently available medicinal products. This *in silico* analysis was designed to use molecular docking to analyze the anti-inflammatory ability of natural compounds and Non-steroidal Anti-inflammatory Drugs (NSAIDs). Curcumin, Gallic acid, Artemisinin, Andrographolide and Rosmarinic acid are natural compounds used and drugs (NSAIDs) such as Indomethacin, Ibuprofen and Flurbiprofen are used in the determination of anti-inflammatory properties.

Anti-inflammatory medications gradually decrease pain by minimising inflammation. People can use these medications for pain, rigidity, swelling, and fever symptoms. NSAID painkilling decreases the direct inflammatory effect on pain nerve stimulation and sensitivity and indirect effect of inflammatory heat and swelling. There is a possibility of side effects from NSAIDs, as in many other drugs. The risk is much higher if you take heavy doses or are aged or ill in general health for a long time. However, NSAIDs normally have less adverse effects than stronger pharmaceutical products. NSAIDs can have side-effects, such as indigestion, sleepiness, dizziness and allergies [3]. NSAIDs raise the risk of fatal adverse reactions to the stomach and intestines (for example, bleeding, ulcers, and perforation of the stomach or intestines). These incidents may be happening at any time without alert. However, NSAIDs normally have less adverse effects than stronger pharmaceutical products. The risk of this adverse occurrence is higher for elderly patients. The overall risk for fatal heart attacks, strokes and associated diseases may be raised with NSAIDs (except low-dose aspirin). This risk will increase with usage period and in patients with underlying cardiovascular risk factor [4]. Indomethacin, Ibuprofen, and Flurbiprofen are NSAIDs used to determine the anti-inflammatory medications. The chemical structure of the NSAIDs is shown in Figure 1.1.

Indomethacin is an anti-inflammatory non-steroid (NSAID) medicine which reduces fever, pain and inflammation. Indomethacin acts by reducing prostaglandin production. Prostaglandins are chemicals produced by the body and causing fibre and inflammatory pain. Indomethacin blocks prostaglandin enzymes and lowers prostaglandin levels thereby decreases the number of people suffering from fever, pain and inflammation [5]. Indomethacin can be used in mild to severe osteoarthritis, arthritis rheumatoid, gouty arthritis or spondylitis ankylosing. Indomethacin is sometimes used to treat bursitis or tendinitis pain in the shoulder [6]. Next, Ibuprofen is an anti-inflammatory non-steroidal medication

(NSAID). It works by reducing hormones which cause swelling and body pain [7]. Ibuprofen acts by blocking prostaglandin production, compounds released by the body in response to disease. The painkilling effects of ibuprofen begin shortly after a dose. It can take longer, sometimes several weeks, for anti-inflammatory effects [8]. Ibuprofen is used to treat pain or inflammation caused by various conditions, such as headache, toothache, back pain, arthritis, menstrual cramps, or mild injuries. It's also available in doses of 200–400 mg as tablets or capsules. If you have rheumatoid arthritis or another form of inflammatory arthritis, higher doses of ibuprofen are available on prescription. Lastly, Flurbiprofen is an anti-inflammatory anti-steroidal medicine (NSAID) and effective for treating fever, pain and body inflammation. Flurbiprofen is used to decrease arthritis pain, swelling, and joint stiffness. This treatment is considered anti-inflammatory non-steroidal medicine (NSAID). Flurbiprofen is an inhibitor of cyclooxygenase (Cox-1 and -2) blocking the production of essential prostaglandins in pain and infection [9]. Flurbiprofen has both analgesic and antipyretic and anti-inflammatory benefits. Flurbiprofen can result in heart attacks and strokes, fluid build-up and heart disease, hypertension and kidney failure. The target protein for these NSAIDs and Natural Compound Ligands are Human Phospholipase A2, Toll-like receptor 4, Interleukin-1 and Cyclooxygenase-2 as shown in Table 1.1.1.



Indomethacin Ibuprofen Flurbiprofen

Figure 1.1: Chemical Structure of NSAIDs

The natural compounds used in this study are curcumin, gallic acid, artemisinin, andrographolide and rosmarinic acid. The chemical structure of the natural compounds is shown in Figure 1.1.2. Curcumin, a polyphenol, has commonly been used as traditional medicines in Asian countries. Curcumin acts mainly through its anti-oxidant and anti-inflammatory mechanisms. It also helps in curing oxidative and inflammatory disorders, metabolic syndrome, arthritis, anxiety and hyperlipidemia. It also is said to support the management of exercise-induced inflammation and muscle aches, thereby improving recovery and subsequent results in active people. Besides, a low dose of curcumin may offer health benefits to people who have not been diagnosed with health conditions [10]. Next, gallic acid is a trihydroxybenzoic acid, it is classified as a phenolic acid. It is found in gallnuts, sumac, witch hazel, tea leaves, oak bark and other plants. There are several benefits effects for gallic acid including antioxidant, anti-inflammatory and antineoplastics. After that, Artemisinin is a