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Features of Anti-Inflammatory Drugs and the Relevance of Creating New Anti-Inflammatory Drugs

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Annotation: The general reaction of the body to injury or infection is called inflammation. A short-term reaction to injury or infection is called an acute inflammatory process. At this stage, the immune system releases a large number of white blood cells to surround and protect the affected area. This leads to redness and swelling. Thus, inflammation is crucial, because without it, simple infections can pose a threat. However, prolonged or persistent inflammation is the main cause of many inflammatory diseases, including cancer. NSAIDs are known as one of the most popular medications due to their ability to reduce pain and inflammation. This confirms their place in the WHO model list of essential medicines. Data on the global burden of disease over the years show that musculoskeletal complications are becoming more common, making the use of NSAIDs inevitable. In addition to their analgesic, anti-inflammatory and antipyretic properties, NSAIDs protect against a number of serious diseases such as cancer and heart attacks. In this regard, despite the increase in the share of biological drugs for the treatment of inflammatory diseases, low-molecular-weight drugs continue to dominate the pharmaceutical industry. Recent advances in deciphering the ability of low-molecular-weight drugs to alter interactions between proteins in vivo have opened up fantastic

opportunities for the development of new low-molecular-weight drugs for the treatment of inflammation and various other diseases.

Keywords: NSAIDs, OTC drug, side effects, inflammatory diseases, COX-1, COX-2, contraindication.

Introduction. As part of their therapeutic action, many nonsteroidal anti-inflammatory drugs (NSAIDs) act on COX isoforms. NSAIDs have become bestsellers in the pharmaceutical industry since the isolation of salicylate from willow bark around the mid-1800s and the subsequent discovery of acetylsalicylate, or aspirin, by Felix Hoffman of Bayer in Germany in 1897. Hippocrates wrote around 500 BC, even before the advent of clinical trials and scientific knowledge, that willow leaves and bark can relieve pain and fever. Subsequently, many generations of scientists, chemists and science enthusiasts put a lot of effort into developing these "miracle drugs". NSAIDs currently account for 5% of all prescribed medications and are among the most common over-the-counter medications worldwide [1,2,3,4]. Traditionally, NSAIDs have been classified according to their chemical properties. Most NSAIDs are the main derivatives of acetic acid, propionic acid, enolic acid, anthranilic acid or salicylic acid. But with the development of science, the classification has also been changed depending on how well they work with cyclooxygenase/prostaglandin endoperoxidase (PGHS) enzymes, the main targets of these drugs. The half-life was also used to classify NSAIDs. However, their functions are almost identical, despite the diversity between classes. NSAIDs are mainly used to treat patients and inflammatory diseases such as chronic pain, rheumatoid arthritis, osteoarthritis, menstrual pain and postoperative conditions. They are also often used as analgesics and antipyretics [5,6,7,8].

In addition, it has already been proven that typical NSAIDs have a strong anti-inflammatory effect compared to acetaminophen, which is an atypical NSAID that does not have an anti-inflammatory effect, but has a weak antipyretic and nonspecific cyclooxygenase/prostaglandin inhibitory effect and other antipyretic analgesics such as opioids. Blindly randomized controlled trials have shown that NSAIDs work better than acetaminophen. In fact, the use of opioid-based painkillers is the cause of some problems related to opioid addiction [9,10,11,12]. Despite the fact that there are separate reports on the effects of these drugs on specific organs in which both PGHS/PG-dependent and independent effects of NSAIDs have been associated with their cytotoxic effect, at the moment there is no comprehensive document describing the results of various randomized trials, meta-analyses, systematic reviews as well as the mechanism of action of NSAIDs and its effect on various organs In this article, we tried to give a general idea of the structure and functions of NSAIDs, with special emphasis on organ damage. The researchers also proposed possible methods for safer use of these drugs, discussing previous studies and the latest research in this area [13,14,15].

The main purpose of the presented manuscript is to conduct a brief analysis of such inconveniences of NSAIDs as side effects, contraindications, toxicity, which are used today in almost all areas of medical practice, and the relevance of their elimination.

Side effects of NSAIDs. NSAIDs have known side effects affecting the liver, hematopoietic system, cardiovascular system, kidneys and gastric mucus. Inhibition of COX-1, which prevents the production of prostaglandins that protect the gastric mucosa, is the main cause of stomach problems. Patients with past peptic ulcer disease are more prone to injury. The use of selective NSAIDs that inhibit COX-2 is better because it is specific to COX-1. COX-1 and COX-2 contribute to the production of prostaglandins, which play a role in renal hemodynamics, which leads to side effects from kidney stops. In people with normal renal function, inhibition of prostaglandin synthesis is not difficult; however, in people with renal insufficiency, these

prostaglandins are more important and can cause problems when reducing prostaglandin levels with NSAIDs. Acute renal failure, impaired water-salt balance, papillary necrosis of the kidneys and nephrotic syndrome or interstitial nephritis are all potential complications [14,15,16,17]. Taking NSAIDs may increase the risk of cardiovascular disease, including myocardial infarction, thromboembolic complications and atrial fibrillation. Side effects from the cardiovascular system are most common when taking NSAIDs such as diclofenac. NSAIDs do not cause liver-related side effects, and hospitalizations due to liver problems are very rare. Diclofenac has the highest hepatotoxicity among other NSAIDs. Due to their antiplatelet activity, hemorrhagic side effects are possible, especially when using non-selective NSAIDs. Patients who have had gastrointestinal ulcers in the past, diseases that reduce platelet activity (for example, hemophilia, thrombocytopenia, Willebrand's disease, etc.), and some perioperative conditions are usually not the cause of this antiplatelet effect. Anaphylactoid reactions affecting the skin and respiratory system, such as urticaria and aspirin asthma, are among the minor side effects of the drug. (Table 1) [17,18,19,20,21].

Table 1. Side effects are possible at the level of organs and systems

№	Organs and systems	There is a possibility of side effects
1.	From the stomach side	Indigestion and other gut complaints, peptic ulcer
2.	From the side of the kidneys	Acute renal failure, impaired water-salt balance, papillary necrosis of the kidneys and nephrotic syndrome/interstitial nephritis
3.	From the cardiovascular system	Myocardial infarction, thromboembolic complications and atrial fibrillation
4.	From the liver	Increasing the level of aminotransferases
5.	Hematological side effects	Hemophilia, thrombocytopenia, Willebrand's disease, etc.
6.	Other minor side effects	Anaphylactoid reactions affecting the skin and respiratory system, such as urticaria and aspirin asthma,
7.	From the side of the brain	Headaches, dizziness, drowsiness

Contraindications, toxity and monitoring of NSAIDs. The package insert states that people with NSAID or salicylate hypersensitivity, as well as those who have had an allergic reaction (such as urticaria, asthma, etc.) after taking NSAIDs, should not use them. With whom coronary artery bypass graft surgery has been performed. While pregnant, in the third trimester. GI bleeding, hypertension, hepatotoxicity, and renal impairment are all signs of NSAID toxicity. Acute NSAID overdose usually has no gastrointestinal symptoms or very mild ones. Acute renal failure, convulsions, coma, and anion gap metabolic acidosis are possible further signs of toxicity consequences. Additionally, by blocking COX-1, which lowers the creation of gastric mucosa, NSAIDs can harm the gastrointestinal tract. Because NSAIDs lower prostaglandin levels, which are necessary for the vasodilation of the renal arterioles, nephrotoxicity may also result from their use. Finally, symptoms of CNS toxicity may include headache, tinnitus, impaired vision, diplopia, nystagmus, sleepiness, and disorientation. A CBC, kidney tests, and a liver panel are all advised forms of surveillance. The American College of Rheumatology has issued these guidelines for use in rheumatoid arthritis patients who use NSAIDs on a regular basis and who do not have any comorbidities or a history of problems. Patients who are not thought to be at high risk for NSAID toxicity are monitored less frequently. However, in patients with hepatic or renal issues, NSAIDs are either contraindicated or their use needs to be monitored. [19,20,21,22,23].

Improving the Results of the Healthcare Team. NSAIDs are widely used by the general public due to their many often encountered indications. Given the numerous potential negative effects on various organ systems, patient education regarding the use of NSAIDs is a crucial aspect of care that doctors must focus on. Physicians, nurses, and pharmacists must closely listen to a patient's

history and educate them about risks and dosage because individuals with certain comorbidities are substantially more likely to experience these side effects. The treating practitioner, whether for a brief or extended period, will start therapy. In addition to checking for any drug-drug interactions, the pharmacist must confirm the dosage and administration [19,20,21,22,23]. In addition to checking for any drug-drug interactions, the pharmacist must confirm the dosage and administration. Pharmacists should also offer patient advice on how to appropriately use their NSAID and prevent side events; this is particularly the case when the patient uses NSAIDs as an OTC drug. In order for the clinician to prescribe NSAID therapy with knowledge, nursing must also carefully record the patient's drug history, including OTC NSAID use. In order to modify the patient's medication as necessary, physicians, pharmacists, and clinicians must all be aware of the warning signs and symptoms of NSAID toxicity or side effects. To guarantee that each patient receives the right dosage for their particular disease and comorbidities—one that is high enough for efficacy but as low as feasible to lower the likelihood of side effects—the healthcare team should collaborate and communicate. NSAID therapy can provide the greatest benefit with the fewest drawbacks when interprofessional collaboration is collaborative [11,12,18,19,20,23].

Discussion. Inflammation is a protective reaction to infection and tissue damage. However, chronic inflammation is crucial for the development of many inflammatory diseases, including cancer. Anti-inflammatory drugs block cyclooxygenase (COX), an enzyme responsible for the production of prostaglandins that cause inflammation. Because they suppress constitutive enzyme oxidative hormone (COX-1) and induced enzyme hormone (COX-2), conventional NSAIDs cause side effects in both the stomach and kidneys. Most selective COX-2 inhibitors (COX-2IB) have no side effects on the stomach. However, if they are used for a long time, they can cause heart problems. Thus, pharmaceutical companies are constantly looking for harmless anti-inflammatory drugs. When it comes to PGE2, which is the main mediator of inflammatory diseases, the development of a method that reduces the level of PGE2 on its own without affecting other metabolites may be an ideal approach for the development of new anti-inflammatory drugs [1,2,3,4,5]. In this direction, various variants of the synthesis of PGE2-mPGES-1 are being studied; degradation of PGE2 using a certain PG dehydrogenase 15-PGDH and blocking its activity using a certain PGE receptor EP4. They are trying to influence both the COX pathway and the LOCH pathway, because leukotrienes formed as a result of the 5-lipoxygenase (5-LOX) pathway also play an important role in the development of inflammation. This analysis addresses three issues: :1) There is a link between NSAIDs and COX-2 inhibitors and possible side effects for the stomach, kidneys and heart; 2) Whether to focus on targets with high or low levels of PGE2; and 3) the status of alternative targets that are being studied for the development of anti-inflammatory drugs without side effects [6,7,8,9].

In conclusion, it should be noted that the discovery and development of anti-inflammatory drugs are mainly based on the effect on prostaglandin biosynthesis. This is done using cyclooxygenases, which limit the formation of prostaglandin E2. Although this method has allowed several drugs to be marketed, it has significant limitations due to undesirable side effects. Thus, there is currently a shift in the search for targets below cyclooxygenases that limit the level of PGE2 or block its specific receptors. In addition, efforts are being made to simultaneously affect the 5-LOX pathway, which promotes the formation of inflammatory leukotrienes [14,15,16,17]. It is obvious that the use of high-throughput screening and fragmentary screening methods in the national approach to drug development may allow us to obtain new low molecular weight ring structures that can be optimized using medical chemistry methods to demonstrate suitable in vivo activity and optimal pharmacokinetic properties. Low-molecular-weight drugs continue to dominate the pharmaceutical industry, despite an increase in the share of biological drugs for the treatment of inflammatory diseases on the market. Exciting opportunities for the development of new low-molecular-weight drugs for the treatment of inflammation and a wide range of diseases have opened up thanks to recent advances in deciphering the ability of low-molecular-weight drugs to alter interactions between proteins in vivo, thus, there is currently a shift in the search for targets

below cyclooxygenases that limit the level of PGE2 or block certain receptors. In addition, efforts are being made to simultaneously target the 5-LOX pathway, which promotes the formation of inflammatory leukotrienes. [3,4,515,17,18].

Conclusion. Thus, one of the most common medications is NSAIDs, which have a wide range of applications. NSAIDs include non-selective COX inhibitors and as well as selective COX-2 inhibitors. It is obvious that the use of high-throughput screening and fragmentary screening methods in the national approach to drug development may allow us to obtain new low-molecular ring structures that can be optimized using medical chemistry methods to demonstrate suitable *in vivo* activity and optimal pharmacokinetic properties.

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