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REVIEW ARTICLE

Investigating Non-Steroidal Anti-Inflammatory Drugs as Potential Cancer Adjuncts: A Novel Approach to Cancer Therapy

Sadaf Alam[1], Leena Anjum[2]*, Muhammad Haneef[3]

[1]Department of Pharmacology, Faculty of Pharmacy & Pharmaceutical Sciences, University of Karachi, Pakistan.
[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy & Pharmaceutical Sciences, University of Karachi, Pakistan.
[3]Department of Pharmacy, Benazir Bhutto Shaheed University, Pakistan.

ABSTRACT

Purpose: This review aims to evaluate the chemo preventive and therapeutic potential of non-steroidal anti-inflammatory drugs (NSAIDs) in cancer management, emphasizing their mechanisms of action and clinical relevance.

Background: Cancer is a leading cause of mortality worldwide, prompting the need for innovative treatments. NSAIDs, particularly selective cyclooxygenase-2 (COX-2) inhibitors, have shown potential as anticancer agents. These drugs reduce inflammation and regulate key biological pathways involved in cancer progression, offering new avenues for prevention and therapy.

Methodology: A comprehensive review of clinical, epidemiological, and experimental studies was conducted to assess the roles of NSAIDs including aspirin, meloxicam, celecoxib, sulindac, naproxen, indomethacin, and piroxicam, in cancer treatment. Key mechanisms such as metastasis reduction, apoptosis induction, tumor invasion inhibition, and suppression of cancer progression, were analyzed.

Results: NSAIDs demonstrate significant anticancer effects by targeting inflammation-mediated pathways. They exhibit promising outcomes in reducing metastasis, promoting apoptosis, and inhibiting tumor invasion and progression. These findings support their potential as both chemopreventive and chemotherapeutic agents.

Conclusion: NSAIDs are promising therapeutic alternatives in cancer treatment, offering significant chemopreventive and therapeutic benefits. However, further clinical studies are required to optimize their application and address potential risks, ensuring safe integration into oncological practice.

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INTRODUCTION

Among the leading reasons of mortality in the globe is cancer. The advances in technology and our growing understanding of human neoplastic illness present opportunities to help lower the mortality from cancer by the discovery of novel treatments[1].

Cancer is one of the prevailing causes of death worldwide, almost 10 million deaths was reported in the year 2020. The most common among them were breast cancer (2.26 million cases), lung cancer (2.21 million cases), colon and rectal cancer (1.93 million cases), prostate cancer (1.41 million cases), skin cancer (1.20 million cases), and stomach cancer (1.09 million cases). It is predicted that in coming years, the death proportion due to cancer may exceed the mortality caused by cardiac diseases[2].

Chemoprevention is a widely recognized strategy to stop the spread of cancer in people with pre-cancerous lesions, high-risk groups with genetic pre-dispositions, or people who have been exposed to environmental carcinogens like cigarette smoke for a long duration. Conversely, chemoprevention requires

extraordinary safety and effectiveness. Nonsteroidal anti-inflammatory medicines (NSAIDs) have been shown through three decades of epidemiological, clinical, and experimental research to suppress carcinogenesis in a variety of tissues and at different phases of the disease's evolution. The use of NSAIDs for cancer chemoprevention is not advised despite the compelling evidence of activity due to the possibility of serious adverse effects on the kidneys, heart, and gastrointestinal tract brought on by the inhibition of cyclooxygenase (COX) and the suppression of physiologically significant prostaglandins. Furthermore, there is an inadequate evidence base on the chemoprophylaxis efficacy of NSAIDs; however, it is unclear if this deficiency stems from resistance[3]. NSAIDs primarily prevent cancer by influencing the eicosanoids' pathway. Many clinical investigations have previously shown that NSAIDs have anti-tumor effect and that long-term use lowers the risk of lung, breast, esophageal, and colorectal malignancies. By disrupting the tumor inflammatory milieu, NSAIDs were able to stop the growth of tumors and demonstrated toxicity and non-specific effects that were less severe than those brought on by traditional chemotherapy[4].

Though cancer is associated with an uncontrolled cell division and DNA mutations leads the focus of medical research on the reduction of tumor size on antiproliferative substances[5]. There must be a balanced between cell death and cell growth for many numerous physiological functions including proper tissue growth and homeostasis. The cell cycle regulates the process of mitosis, which splits all body cells. Programmed cell death, or apoptosis is the process of eliminating undesirable, damaged or hazardous cell. The cell cycle and apoptosis are linked processes that are governed by different factors[6]. The equilibrium between apoptosis and production is crucial for regulating the growth of tumors. A net rise in the quantity of tumor cells indicates the advancement of tumor growth. This may be the result of either reduced apoptosis, enhanced proliferation, or both[7].

This review emphases the role of NSAIDS in Cancer treatment by discussing the mechanism of action, inflammatory factors, metastasis, apoptosis, tumor invasion and inhibition of cancer progression to explore this class as safe and effective option in patients of cancer.

MATERIALS AND METHODS

Existing Use of NSAIDs in Cancer

NSAIDs are the most frequently prescribed drugs worldwide. They are made up of a class of medications with analgesic, antipyretic and anti-inflammatory effects that are used to treat, pain, fever and inflammation. In the clinical setting, they are helpful in reducing pain associated with a variety of ailments, including arthritic, menstrual, and surgical pain. These medications are well-known anti-inflammatory treatments that work by preventing the cyclooxygenase (COX) enzyme from synthesizing prostaglandins. Research over the past few decades has explored the role of NSAIDs in cancer treatment and prevention[8]. Studies suggest that NSAIDs may have a correlation with cancer due to their chemo preventive properties. This is linked to the inhibition of prostaglandin synthesis through the suppression of the activation of COX-1 and COX-2, two cyclooxygenase isoenzymes that are found to express more often in various cancer types. The COX enzyme is important in human body tumor, encompassing the cardiovascular, neuronal, renal, immunological, gastrointestinal, and reproductive systems, has been linked to aberrant expression in numerous tumor types, including those of the prostate, breast, pancreas, lungs, skin, bladder, head and neck. Moreover, NSAIDs chemo preventive activity through the inhibition of COX enzymes, which are overexpressed in many cancer cell lines and in charge of prostaglandin synthesis. Furthermore, the anticancer effects of NSAIDs are demonstrated by the induction of apoptosis, the inhibition of nuclear factor kappa B (NF-κB) factor, which controls immunity and inflammation and inhibits apoptosis induced by cellular stress, and the regulation of tumor suppressor genes[9].

Mechanism of NSAIDs Anti-Tumor Action

COX-1 and COX-2 are the two distinct COX isoforms that are now recognized. Most tissues constitutively generate COX-1, whereas COX-2 is mostly associated with pathological processes and is triggered by inflammatory stimuli, mitogens, or growth factors. Common NSAIDs for example ibuprofen, aspirin, indomethacin and sulindac, inhibit both Cyclooxygenase enzymes; however, aspirin has a distinctive mechanism that irreversibly acetylate serine residue of both enzymes in catalytic domain. Upon realizing that COX-2 is the focal moderator of inflammation, a novel class of inhibitors bearing COX-2 selectivity (Coxibs) was created as a result users were able to avoid the Gastrointestinal and nephritic toxicities associated with nonselective NSAIDs[3]. The overexpression of COX-2 in many forms of solid tumors is one of the compelling arguments in favor of the involvement of COX enzymes in malignancies. One potential contributing factor to cancer is the peroxidase portion of COX enzymes. Because it promotes inflammation and oxidative stress, the peroxidase domain of COX enzymes, especially COX-2, is crucial in the development of cancer. This peroxidase activity produces lipid peroxidation products and reactive oxygen species (ROS), which can damage DNA and accelerate the growth of tumors. Furthermore, COX-2 intensifies the inflammatory milieu that facilitates angiogenesis, tumor development, and immune evasion[10]. By reducing these effects,

inhibitors that target COX-2 peroxidase function-such as NSAIDs are thought to be promising cancer-prevention treatments[11].

Furthermore, the initiation of tumors[11] in the mammary gland epithelial cells has been associated with the elevated action of COX-2. Increased angiogenesis, improved tumor cell motility and invasion with decreased antitumor immunity is found to be associated with COX-2 overexpression in rodents breast cancer models with reduced mammary tumorigenesis and metastasis. Furthermore, in human breast cancer clinical data anticipated with similar functions for COX-2 because of the correlation between COX-2 overexpression with reduced disease free and overall survival. Moreover, the COX enzymes are inhibited by NSAIDs which can lower the risk of breast cancer[12]. Additionally, it has also been connected to the development of intestinal epithelial cells resistance to induced apoptosis. Also, excessive COX-2 promotes metastasis and angiogenesis, activates pro-carcinogen, and slows down apoptosis. Therefore, the reduction of metastasis, angiogenesis, and NF-kB leads to COX inhibitory anticancer action. As pro-angiogenic factors like VEGF are expressed more frequently when NF-kB is activated, new blood vessel creation in tumors is dependent on these factors for angiogenesis to occur. This process facilitates the spread and growth of tumors[10]. Angiogenic signaling is increased because of COX-2 activity enhancing NF-kB. One of the ways that COX inhibitors contribute to their anticancer effects is by lowering COX-2, which also reduces NF-kB activation and VEGF levels and angiogenesis[11].

NSAIDs prevented tumor development in vivo and triggered apoptosis (Figure **1**). Numerous results from investigational animal models, including transgenic or carcinogen-induced models of breast colorectal, and other cancers, corroborate the epidemiologic evidence that NSAIDs lower the chance of getting cancer. Narisawa *et al*. demonstrated that studies by Pollard, Luckert and colleagues, which detailed the inhibitory effects of indomethacin on carcinogen-induced intestinal tumors, are among the earliest reports of the anticancer action of NSAIDs in rodent models[13]. NSAIDs from various classes have been shown in researches to have antitumor efficaciousness against colorectal carcinogenesis[14,15]. Adenomatous polyposis coli[16,17] and β-catenin mutations closely resemble real colorectal cancer, and this is demonstrated using the rodent azoxymethane carcinogen model in many of these investigations[3].

Apart, apoptosis induction was facilitated by Akt inhibition[18]. NSAIDs work by inhibiting the activation of Akt, a protein that normally aids in cell survival, causing cell death (apoptosis) and reducing tumor growth. Normally, signals that stop apoptosis activate Akt[19]. Pro-apoptotic proteins like Bad and Bax can cause cell death, but NSAIDs stop this activation by preventing Akt from being phosphorylated. These proteins cause the cell-degrading enzymes known as caspases to become active[20]. In tumors, where Akt is often overactive, NSAIDs restore the process of apoptosis, leading to reduced tumor growth[21].

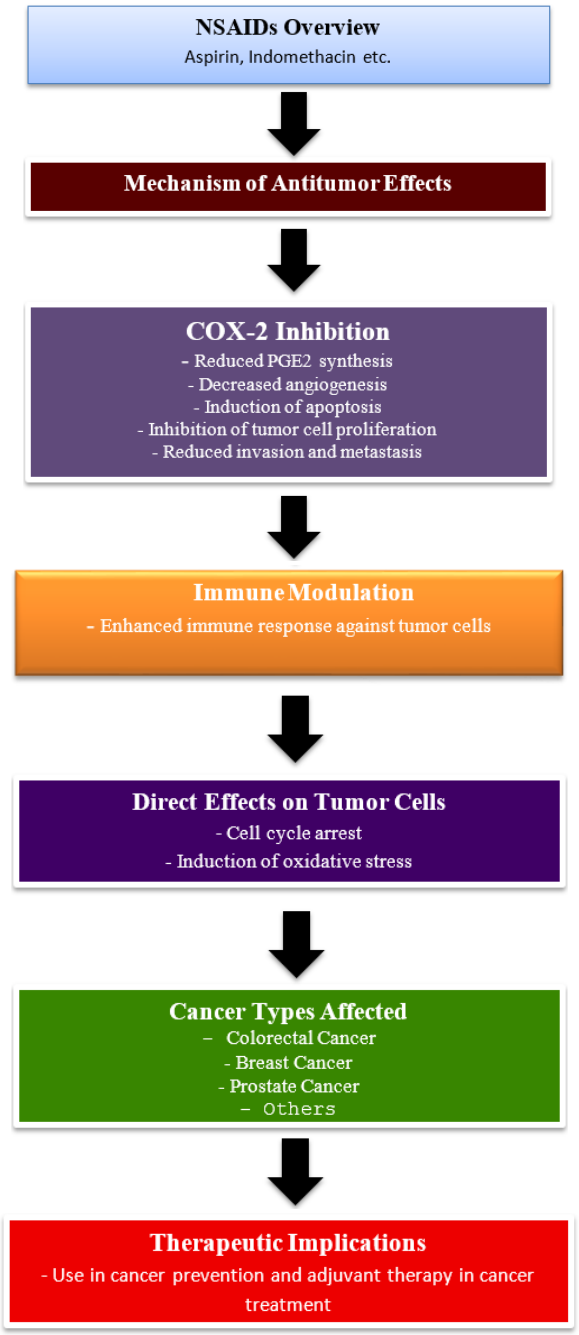

Figure 1. NSAIDs Mechanism of Working as an Antitumor Agent[21,22].

Role of Non-Steroidal Anti-Inflammatory Medications in Cancer

NSAIDs play a vital role in cancer prevention and symptoms management. Drugs including Aspirin, Meloxicam, Celecoxib, Sulindac, Indomethacin, Piroxicam found to be active in chemoprevention and therapeutics.

Aspirin

Since nonsteroidal anti-inflammatory medications (NSAIDs) inhibited chemical-induced carcinogenesis, aspirin has been used in cancer therapy. The main mechanism of NSAIDs, suppression of COX, was thought to be involved, however the exact mechanisms remained unknown[23]. The U.S. Preventive Services Task Force suggested aspirin in the 1990s as a way to prevent non-high-risk colorectal cancer[24].

Aspirin has been shown in numerous clinical studies to offer protection against various cancers, including colorectal cancer. As a result, the antiplatelet activity of aspirin is central to its antitumor efficacy, with benefits being detected low-dose, at least 75mg daily, the same dose used to prevent cardiovascular disease. Aspirin acts by completely and persistently inhibiting cyclooxygenase COX-1 in platelets (in the pre-systemic circulation) at modest dosages administered every 24 hours. However, it also has a limited and quickly reversible inhibitory impact on COX-2 and/or COX-1 produced in nucleated cells[25]. An increased EGFR was observed in 80% of individuals with Familial adenomatous polyposis (FAP) patients; however, regular aspirin use can reduce its level (patients taking two or more tablet of aspirin tablets 325mg per week within last 12 months were categorized as regular aspirin users and whose consumption of less aspirin were classified as aspirin non-users). Additionally, they noticed that the elevated COX-2 activates transcription factors works by binding to the EGFR promoter and activate protein-1, activating proto-oncogenes that might further encourage the accumulation of EGFR cells in cells and their eventual transition into malignant ones. These results were obtained in patients with co-located EGFR and COX-2 who had familial multiple adenomas[26]. Moreover, NSAIDs bearing protection against breast carcinoma. Acetylsalicylic acid reduced the risk of breast cancers, in situ tumors, in hormone receptor-positive, and postmenopausal females. Acetylsalicylic acid in a dose of 325 mg/day for above 3 years have been linked with diminished risk of breast cancer but the relationship between usage of NSAID and chances of developing breast cancer is multifaceted and contrary. Research claims that hormonal consequence has no effect whereas others specify the conflicting. Briefly, NSAIDs may relate to a lessening risk and mortality in various hormone positive subtypes and an increase in others hormone-negative subtypes[27]. Aspirin may prevent and treat a number of human malignancies, including as colorectal, gastric, and lung cancers, in addition to HCC, according to a growing body of studies[28].

Meloxicam

The selective COX-2 inhibitor meloxicam has the greatest anticancer effect on human ovarian cancer that did not have any negative gastrointestinal side effects. Studies suggested that COX-2 potential involvement in several processes related to tumor growth and carcinogenesis. The anticancer impact may be explained by NSAIDs suppression of COX-2 activity, which prevents these activities.COX-2 expression may be crucial for the emergence of ovarian cancer, meloxicam is a selective COX-2 inhibitor. Meloxicam treatment caused considerable suppression of OVCAR-3 tumors and decreased COX-2 expression in tumors via 2.5-fold compared with untreated tumors. It is also reported to reduced micro vessel density and induced apoptosis were achieved in solid OVCAR-3 tumors treated meloxicam[29].

Celecoxib and Sulindac

Sulindac is thought to be the most potent NSAID and COX-2 inhibitor. Sulindac has been shown in several trials to be a highly effective cancer chemo preventive drug in a variety of animal models at far lower doses than those required for celecoxib[30]. When sulindac was administered to patients with familial adenomatous polyposis (FAP), the number of colonic adenomas decreased. Gurpinar *et al.* highlight those studies, provided the first clinical proof of action for the treatment of precancerous diseases. Subsequently, sulindac at a dose of 300–400 mg per day was found to reduce adenomas in FAP patients by up to 71% over a 4–6-month treatment period, according to three randomized clinical trials[3].

Naproxen

Naproxen, a derivative of propionic acid used for the treatment of various pains and injuries. Apart from its anti-inflammatory properties, naproxen has drawn interest from researchers in recent years for its other pharmacological properties, including its antimicrobial and anticancer properties. The COX-2 enzyme is inhibited by naproxen, demonstrating its action[31]. Particularly with respect to cancers where COX-2 is abundantly expressed, such colorectal and breast cancers, the potential of COX-2 inhibitors like naproxen to postpone or prevent the beginning of cancers is of interest[26].

Indomethacin

It was shown that indomethacin and the other NSAIDs had potent anticancer action against a variety of cancer cell types both in vitro and in vivo. Furthermore, a link has been demonstrated by

epidemiological research between the use of these drugs and a decreased risk of cancer. Among the many ways in which indomethacin demonstrates its anticancer qualities are by inhibiting carcinogenesis through immune system stimulation and blocking angiogenesis, as well as suppressing proliferation by inducing apoptosis in tumor cells. The mechanism underlying the anticancer effect underlying this drug is the decrease of PGE2, a prostaglandin that is produced by COX-2 bis-oxygenates arachidonic acid. Through a variety of cell signaling pathways, PGE2 promotes cell proliferation, cell cycle progression, and oncogenic gene activation, which ultimately raises proliferative proteins. Recent research on variety of cancer cell types, including colorectal carcinoma (CRC) supported indomethacin's ability to lower antiapoptotic protein levels and slow down tumor growth by processes that do not require COX[32]. Huang *et al.* discovered that using both indomethacin and Adriamycin together can greatly reduce the growth of tumor cells in glioma cells cultured in vitro compared to using indomethacin alone[20]. Moreover, it considerably enhances the antitumor effect of chemotherapeutic medicines by downregulating the expression of MDR1, ABCG2 and MRP1, which were considered tumor-related resistance genes. Besides, indomethacin increases the sensitivity of colon cancer cells to chemotherapy medications in additive to downregulating the resistance genes. One popular medication used in cancer chemotherapy is 5-fluorouracil (5Fu). It is found that 80% of the 5Fu in the patient's body could be converted by dihydropyridine dehydrogenase into 5, 6-dihydro-5-fluorouracil and lost its action. Additionally, by blocking the activity of dihydropyridine dehydrogenase, indomethacin raises the concentration of 5Fu, which may increase the toxicity of 5Fu to tumor cells[26].

Piroxicam

Piroxicam is prescribed to treat the symptoms of degenerative and inflammatory rheumatic disorder[33]. It has chemo preventive and chemotherapeutic actions in animal models and animal cell cultures. In addition to being a potent anti-inflammatory, piroxicam has been shown in various canine cancer cell lines and animal models to exhibit chemo preventive and chemo suppressive properties. Piroxicam has been demonstrated to cause apoptosis in human oral squamous cell carcinoma (OSCC) when combined with Masitinib and in human malignant mesothelioma cell lines when combined with cisplatin[34]. Table **1** shows mode of actions of different NSAIDS in suppression of tumors.

Table 1. Mechanisms of NSAIDs Anti-Tumor Effects.

NSAIDs	Mechanisms of Anti-Tumor Effects
Aspirin	Reduces the production of prostaglandins by inhibiting the COX-1 and COX-2 enzymes. Promotes apoptosis and suppresses platelet aggregation and angiogenesis, which may stop metastasis, lowers oxidative stress and modifies NF-κB signaling in cancer cells[35].
Meloxicam	Selective inhibition of COX-2, lowering prostaglandin E2 synthesis and inflammation. It suppresses angiogenesis and triggers apoptosis. Potential to reduce the expansion and invasion of tumor cells by adjusting immune response and matrix metalloproteinases[36].
Celecoxib	Selective suppression of COX-2 reduces the invasion of malignant cells, stops angiogenesis, and triggers apoptosis. Inhibits the β-catenin and NF-κB signaling pathways, which decreases cell growth and increases cell death[37].
Sulindac	Limits tumor growth by changing β-catenin signaling, inhibits COX-1 and COX-2 enzymes, activates mitochondrial pathways to cause apoptosis, and decreases tumor invasion by blocking matrix metalloproteinases (MMPs)[36].
Naproxen	Inhibits the production of prostaglandins by COX-1 and COX-2, demonstrates anti-angiogenic qualities, inhibits tumors growth, and causes cancer cells to undergo apoptosis. It minimizes inflammation and oxidative stress in cancers[35].
Indomethacin	The non-selective COX inhibitor suppresses the production of prostaglandins, triggers apoptosis, and prevents the growth of new tumor angiogenesis. Also lowers inflammation and modifies immunological response has been demonstrated to prevent colon cancer cells from proliferating[38].
Piroxicam	Non-selective COX inhibition causes apoptosis, suppresses angiogenesis, lowers immune evasion in tumors, and slows tumor development by blocking prostaglandin synthesis. Reactive oxygen species (ROS) in cancer cells may also be modulated[36].

CONCLUSION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the symptomatic management of pain and fever in a range of clinical settings. Much research has looked at the anticancer effects of these medications because of their anti-inflammatory qualities. This is due to the long-standing association between carcinogenesis and chronic inflammation. Anti-inflammatory medications are thought to be involved in the prevention and treatment of cancer. These medications have been linked to a lower cancer risk in several cancer types, including breast, prostate, colorectal, ovarian, and head and neck cancers, according to several epidemiologic studies.

NSAIDs operate variety of cell signaling pathways that are involved in tumor malignant phenotype maintenance, proliferation, apoptosis, invasion, angiogenesis, and host immune response. Furthermore, NSAIDs could prevent cancer through a variety of molecular and cellular processes. They inhibit inflammatory substances that promote tumor growth and induce programmed cell death (apoptosis). Additionally, NSAIDs can reduce angiogenesis, the formation of new blood vessels, and enhance the immune response against cancer cells.

Overall, NSAIDs have attracted a lot of attention in the fields of chemoprevention and cancer treatment and offers a chance to discover further novel, safer, and more effective derivatives for future.

DECLARATION

We, the authors hereby declare that this work has been reviewed and written originally and has not been published before in any form. All sources of information have been properly cited.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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