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REVIEW

Looking at NSAIDs from a historical perspective and their current status in drug repurposing for cancer treatment and prevention

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently prescribed drug classes with wide therapeutic applications over the centuries. Starting from the use of salicylate-containing willow leaves to the recent rise and fall of highly selective cyclooxygenase-2 (COX-2) inhibitors and the latest dual-acting anti-inflammatory molecules, they have displayed a rapid and ongoing evolution. Despite the enormous advances in the last twenty years, investigators are still in search of the design and development of more potent and safer therapy against inflammatory conditions. This challenge has been increasingly attractive as the emergence of inflammation as a common seed and unifying mechanism for most chronic diseases. Indeed, this fact put the NSAIDs in the spotlight for repurposing against inflammation-related disorders. This review attempts to present a historical perspective on the evolution of NSAIDs, regarding their COX-dependent/independent mode of actions, structural and mechanism-based classifications, and adverse effects. Additionally, a systematic review of previous studies was carried out to show the current situation in drug repurposing, particularly in cancers associated with the GI tract such as gastric and colorectal carcinoma. In the case of non-GI-related cancers, preclinical studies elucidating the effects and modes of action were collected and summarized.

Keywords NSAIDs · Inflammation · Prostaglandins · Cancer · Drug repurposing

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Abbreviations

NSAIDs	Non-steroidal anti-inflammatory drugs
PG	Prostaglandin
COX	Cyclooxygenase
TxA	Thromboxane
PGHS	Prostaglandin H synthase
AA	Arachidonic acid
ER	Endoplasmic reticulum
GI	Gastrointestinal
nsNSAIDs	Non-selective COX inhibitors
LDL	Low-density lipoprotein
LOXs	Lipoxygenases
5-HPETE	5-Hydroperoxy-eicosatetraenoic acid
LTA_4	Leukotriene A_4
LTB_4	Leukotriene B_4
IL-1	Interleukin 1
TNF-α	Tumor necrosis factor alpha
DAAIDs	Dual acting anti-inflammatory drugs
FDA	US Food and Drug Administration
NF-κB	Nuclear factor-kappa B
MMPs	Matrix metalloproteinases
AP-1	Activator protein 1
PDE	Phosphodiesterase
ACE2	Angiotensin-converting enzyme 2
FAP	Familial adenomatous polyposis
LS	Lynch syndrome
DEGs	Differentially expressed genes

The origin and development of NSAIDs: a journey to the past

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most prescribed drug classes for ones suffering from pain, fever, and inflammation. Daily, over 30 million aspirin or non-aspirin NSAIDs are consumed consciously or unconsciously (Emery 2001; Bjarnason et al. 2018). Aspirin™, appointed as the progenitor of NSAIDs, has been the most widely utilized pharmaceutical for over 120 years (Desborough and Keeling 2017). The origin of aspirin or non-aspirin NSAIDs is based on serendipitous discoveries in ancient times (Fig. 1). In the journey to the past, the use of salicylate-containing willow leaves (Salix species) to treat inflammatory rheumatic diseases dates back to the Sumerians (Montinari et al. 2019). The importance of the willow leaf against inflammatory symptoms could be also noted in the Ebers Papyrus (1534 B.C.) (Bryan 1974). Years later, the Greek physician Hippocrates (400 B.C.), the father of medicine, suggested the use of leaves and bark extracts of the Salix plants for the relief of pain and fever. Moreover, a number of the reports recorded by Pliny the Elder (23 CE),

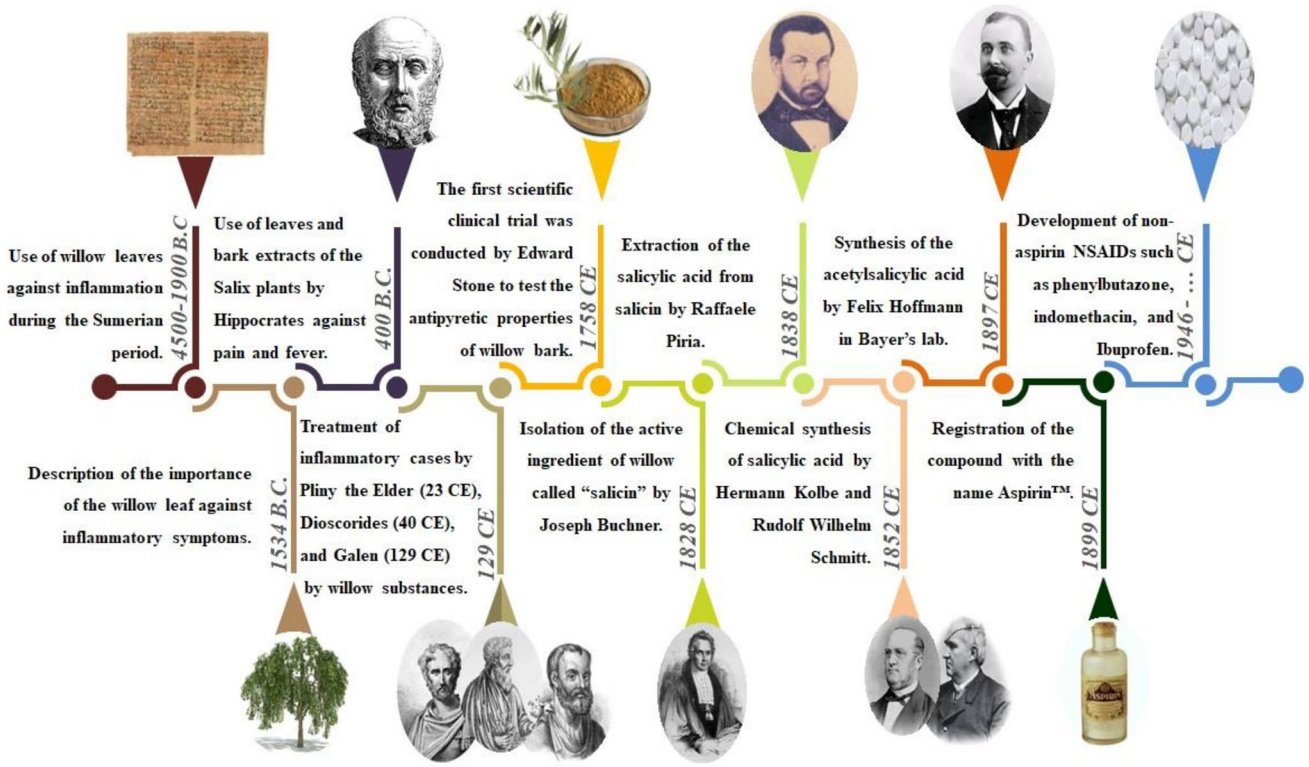

Fig. 1 The milestones in the development of aspirin or non-aspirin NSAIDs in chronological order

Dioscorides (40 CE), and Galen (129 CE) emphasizing the medicinal potency of these extracts have been transmitted from generation to generation (Lichterman 2004). These pre-records paved the way for the clinical application of willow bark extract on 50 patients with agues or fever in the seventeenth century. Accordingly, the results of the trial were presented by Edward Stone, who is the first author recording the healing potency of willow bark as an antipyretic in a scientific manner (Stone 1764). Owing to developments in the fields of chemistry, the isolation of the active ingredient of willow called "salicin" was carried out by German pharmacologist Joseph Buchner in the mid-late nineteenth century (Vane and Botting 1992). A few years later, Italian chemist, Raffaele Piria found a way to extract the salicylic acid, which is the primary compound for the synthesis of aspirin from salicin (Piria 1838).

In 1958, German chemist Hermann Kolbe and his assistant Rudolf Wilhelm Schmitt achieved a significant breakthrough in the chemical synthesis of salicylic acid (Sneader 2005). As a result of its production at an industrial scale, synthetic salicylate was examined by several clinical trials in the same years. The effectiveness of the compound encouraged further studies for the development of salicylate derivatives with diminished adverse effects. In Bayer's lab (1897), pharmaceutical chemist Felix Hoffmann discovered the reaction conditions yielding acetylsalicylic acid (Zündorf and Bayer AG 1997). This pure, stable, and cheap compound was patented by Bayer AG and manufactured in tablet form named Aspirin™. Although years have passed, approximately 100 billion standard aspirin tablets are still marketed each year due to their potent anti-inflammatory, antipyretic, and antiplatelet therapeutic actions (Bjarnason et al. 2018; Casey 2019). Both clinical outcomes and the success of the aspirin in the pharmaceutical industry led to the development of classical NSAIDs. Eventually, drugs such as phenylbutazone, indomethacin, and ibuprofen hit the markets in the pre-prostaglandin (PG) era (Desborough and Keeling 2017).

The mystery behind the action mechanism of aspirin and a group of NSAIDs was satisfactorily unraveled for the first time by the efforts of John R. Vane and his colleagues in 1971 (Piper and Vane 1969; Vane 1971). In their study, it was demonstrated that these compounds inhibit the biosynthesis of PG in a dose-dependent manner (Vane 1971). Additionally, subsequent studies conducted by Vane and Moncada enabled the discovery of prostacyclins. In 1982, due to his discoveries concerning "prostaglandins and related biologically active substances" Vane shared the Nobel Prize in Physiology and Medicine with Samuelsson and Bergstrom. Finally, the puzzle was completed with the identification of the biological target of aspirin and NSAIDs by Hemler et al. demonstrating cyclooxygenase (COX) as the principal enzyme in the synthesis of PG. (Hemler and Lands 1976). In the light of this discovery as well as with the advances in molecular biology, the classification and evaluation process of NSAIDs have been reshaped towards the concept of understanding their biological target(s) instead of chemical and structural similarities. Additionally, the molecular mechanisms for the adverse effects of NSAIDs have been revealed.

COXs as biological target of NSAIDs

The basic action mode of NSAIDs is based on the inhibition of COX enzymes thereby reducing the release of PGs and thromboxane (TxA). When Hemler et al. identified the constitutive COX enzyme, also termed as prostaglandin H synthase (PGHS), in 1976 for the first time; it was not known the existence of different COX isoforms. In the late 1980s–early 1990s, a second isoform of the enzyme (COX-2) was identified, isolated, and cloned (Kujubu et al. 1991). Both COX isoforms share a common role in arachidonic acid (AA) metabolism in which bioactive PG species are synthesized from arachidonate. They have not only similarities in the function, but also in the structure. The comparative analysis of these genes also revealed almost 60–65% amino-acid identity with each other in the same species and 85–90% similarity among different species (Yokoyama et al. 1988). As represented in Fig. 2, another common feature of COXs is their subcellular localizations. Both are membrane-bound enzymes found mainly on the luminal side of the endoplasmic reticulum (ER); however, COX-2 is also located on the nuclear membrane (Chandrasekharan and Simmons 2004).

The main differences between these isoenzymes are their levels and tissues in which they are expressed in the body. The COX-1 is constitutively expressed in various tissues at low levels for the maintenance of the synthesis of physiologically important prostanoids, which are

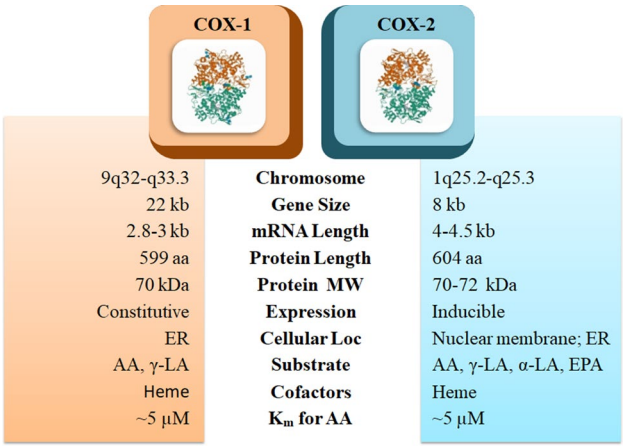

Fig. 2 The comparison of the features of human COX isoenzymes

essential for the gastrointestinal cytoprotection, regulation of renal blood flow, improved organ perfusion as well as a healthy pregnancy (Bertolini et al. 2001). In contrast, the expression of COX-2 is up-regulated in cells (mainly in monocytes, macrophages, synovial micro vessel endothelial cells, chondrocytes, and osteoblasts) by several stimulants including bacterial endotoxins, pro-inflammatory cytokines, and growth factors (de Brum-Fernandes et al. 1994; Szczepanski et al. 1994; Berenbaum et al. 1996). Sustained activation of COX-2 is associated with the exaggerated production of inflammatory factors/mediators and pain-related PGs.

Understanding the molecular mechanisms, classifications, and adverse effects of NSAIDs

The production of the PGs and TxAs depends on the presence of AA at the site of action. When the cell is triggered in response to various stimuli, the enzymes called secretory and cytoplasmic phospholipases A2 balancing the eicosanoid levels, are activated to convert the membrane-bound arachidonate into free AA (Fig. 3). The release of AA induces COX pathways in which these molecules are oxygenated by COXs to yield prostaglandin G_2. Immediately after, this molecule is catalyzed by peroxidase into prostaglandin H_2 (PGH_2) (Fig. 3a), which is a substrate for the cell-specific enzymes to generate bioactive PG species: PGD_2, PGE_2, $PGF_{2\alpha}$, prostacyclin (PGI_2), and thromboxane A_2 (TxA_2) as shown in Fig. 3b (Smith and Langenbach 2001).

The previous pieces of evidence suggested that in the AA cascade, COX-2 derived prostanoids such as PGE_2 and PGI_2, drastically elevated at the inflamed tissues, contribute extensively to inflammation, pain and, fever response by increasing local blood flow, vascular permeability, leukocyte infiltration, and heat production (Smyth et al. 2009; Ricciotti and FitzGerald 2011; Aoki and Narumiya 2012). On the other hand, COX-1-derived prostanoids are physiological regulators of the digestive mucosal barrier, renal homeostasis, and platelet aggregation. For this reason, undesired inhibition of COX-1 during long-term NSAIDs therapy leads to a dramatic reduction in the gastroprotective PGs levels resulting in severe adverse effects including stomach erosions, bleeding, and perforation in gastrointestinal tracts—so much so that it is estimated that 15.3 people pass away per 100,000 NSAID users in Europe (Lanas et al. 2006). These emerging concerns have prompted researchers to develop an alternative approach to treat and prevent inflammation-based diseases. Selective COX-2 inhibition was thought to

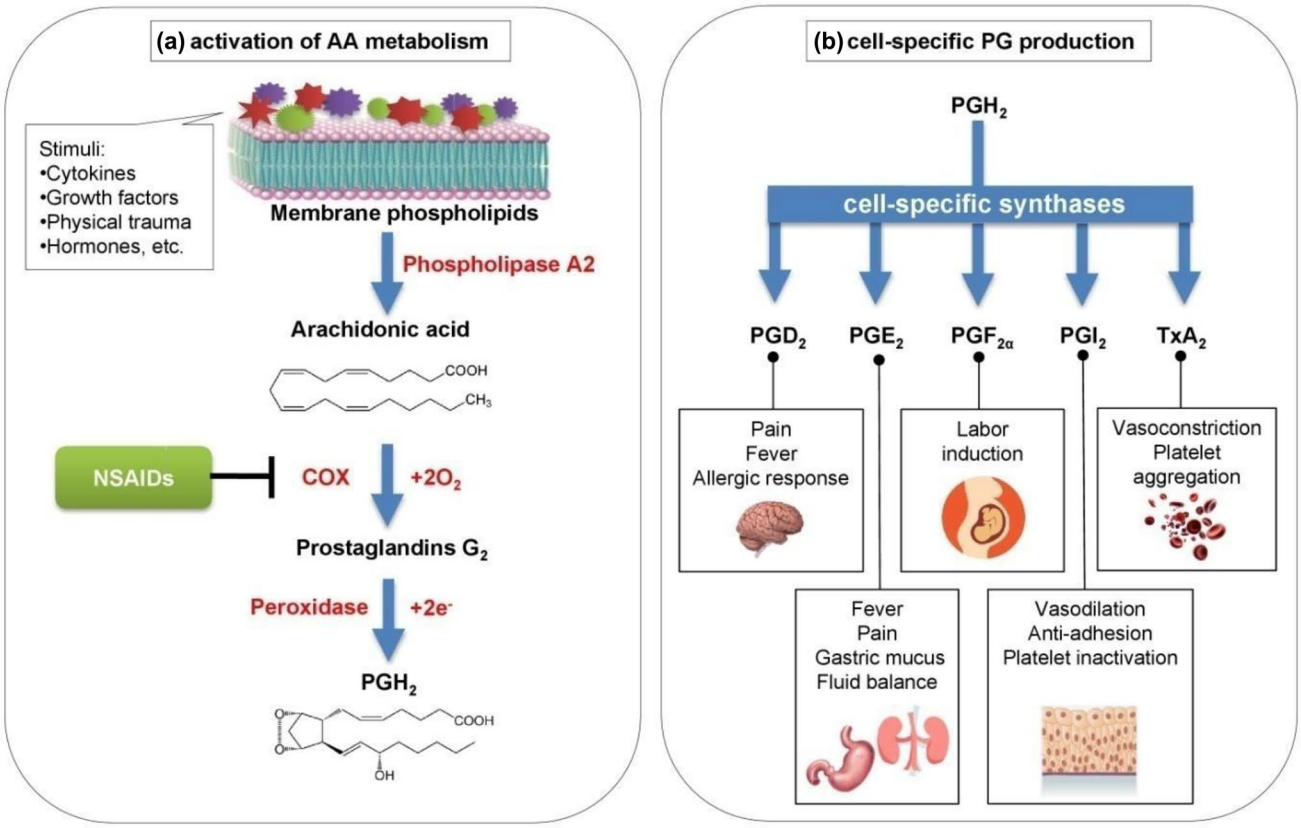

Fig. 3 The synthesis of prostaglandin species from membrane-bound arachidonate via COX-1/COX-2 isoform catalysis

be a promising strategy; the inhibition of inducible COX prevents the release of excess amounts of pro-inflammatory PGE_2, thus sparing the gastroprotective prostaglandin synthesis mediated by constitutive COX.

The elucidation of the structures of COXs was one of the most important milestones for the discovery of selective COX-2 inhibitors (Chandrasekharan and Simmons 2004). These studies displayed that COX-1 and COX-2 have structural similarities and highly conserved active sites where they interact with the inhibitors. However, further mutagenesis experiments by Gierse et al., indicated that a single amino acid change in COX-2 (Val to Ile) transforms it to a COX-1 inhibitory profile for COX-2 selective inhibitors. Considering these findings, it might be proposed that having Val at the 509th position provides a larger region allowing the selective electrostatic interactions for compounds fitting at the mouth of the active site of COX-2 (Gierse et al. 1996).

The drugs (Fig. 4) with high selectivity on COX-2 initially exhibited more favorable safety profiles regarding gastrointestinal (GI) health as compared to the classical NSAIDs. The most popular selective COX-2 inhibitors, the class of ***cox***-inhibit; coxibs (celecoxib, etoricoxib, parecoxib, rofecoxib, valdecoxib, lumiracoxib), were preferred to be utilized in clinics. Despite the early success of these drugs, many cardiovascular problems have been reported after marketing. Further studies explained the underlying reason as the imbalance in the synthesis of prothrombotic TxA_2 (mainly mediated by COX-1) and antithrombotic PGI_2 (mainly mediated by COX-2) (Rainsford 2007). Clinical data suggest that NSAIDs with COX-2 selectivity have lost the cardio-friendly properties of classical NSAIDs. Accordingly, the drugs rofecoxib and valdecoxib were withdrawn from marketing due to side effects in the cardiovascular system. For the same occasion, etoricoxib is not approved in several countries. Moreover, another drug in the coxib group named lumiracoxib was withdrawn from marketing because of severe liver toxicity (Rao and Knaus 2008). Apart from others, celecoxib is allowed to remain in pharmacies with related labels highlighting the potential adverse actions.

Later, research studies presented shreds of evidence for the involvement of two isoforms both in homeostasis and inflammatory processes. Accordingly, in the early phases of the inflammation, COX-1 activity seems to be predominant until COX-2 is upregulated and takes the lead for the synthesis of pro-inflammatory PGs (Smyth et al. 2009; Ricciotti and FitzGerald 2011). Moreover, COX-2 is constitutively expressed in particular organs such as the kidney, therefore selective COX-2 inhibition has been found to be associated with reduced glomerular filtration and renal blood flow resulting in edema and kidney degeneration (Tegeder et al. 2001). This novel finding has motivated clinicians to convert treatment strategies towards the use of relatively selective, i.e., "preferential COX-2 inhibitors" or/and non-selective COX inhibitors (nsNSAIDs) (Fig. 4). While highly selective coxibs exhibit 200–300-fold selectivity for COX-2 isoform at approved therapeutic doses, preferential inhibitors inhibit COX-2 with 5–50-fold selectivity (Fig. 4). As a result of this distinction, it is thought that preferential inhibitors might be better tolerated than other NSAIDs with particular reference to GI and cardiovascular system associated problems. However, it is increasingly being realized that NSAID-related side effects are not only based on COX selectivity but also vary by other factors.

Other potential mechanisms that might influence the safety and toxicity profiles of NSAIDs especially considering the long-term use of these compounds in the treatment of chronic pain and inflammatory conditions can be molecular structures, p*K*a values, and COX-independent/off-target effects.

Regarding chemical structures, NSAIDs fall into four broad categories: Diaryl-substituted pyrazoles/furanones (generally coxibs), sulphonamides (contains only nimesulide), carboxamides/oxicams (piroxicam/meloxicam), and carboxylic acids (aspirin, naproxen, diclofenac, ibuprofen, indomethacin, ketoprofen, flurbiprofen). All nsNSAIDs have carboxylic acid in their structures (Fig. 4). Indeed, a huge number of NSAIDs are inherently acidic/or weakly acidic with pKa values changing between 3.50 and 6.86 except for some coxibs and nabumetone (Calatayud and Esplugues 2016). Acidic NSAIDs have a lipophilic nature allowing them to interact with phospholipids found on the cellular membrane as well as increased cellular accumulation. This might result in loss of membrane and intracellular integrity, finally leading to direct damage to surface epithelium and increased intestinal permeability (Bjarnason and Takeuchi 2009; Ho et al. 2018). Besides acidic nature, the presence of certain chemical moieties can represent a risk factor for the development of side effects in case of long-term use. For example, some coxibs such as celecoxib, etoricoxib, and rofecoxib have sulfonyl groups which may have a tendency to oxidize biological lipids such as low-density lipoprotein (LDL), therefore presenting a risk for the development of cardiovascular diseases (Ho et al. 2018).

Not only COXs but also lipoxygenases (LOXs) are key enzymes in the regulation of inflammation as illustrated in Fig. 5. While COXs convert AA into cell-specific PGs species, in the LOX pathway, the same substrate is catalyzed for the biosynthesis of leukotrienes (Natarajan and Nadler 2004). LOXs are responsible for the insertion of the O_2 molecule in a specific site of AA. There are mainly four types of LOXs: 5-, 8-, 12- and 15-LOX, wherein the number indicates the position of the insertion site (Brash 1999). Under the inflammatory condition, 5-LOX catalyzes the oxidation reaction of AA into 5-hydroperoxy-eicosatetraenoic acid (5-HPETE) and this molecule is metabolized into leukotriene A_4 (LTA_4). One of the fates of LTA_4 is the hydrolysis

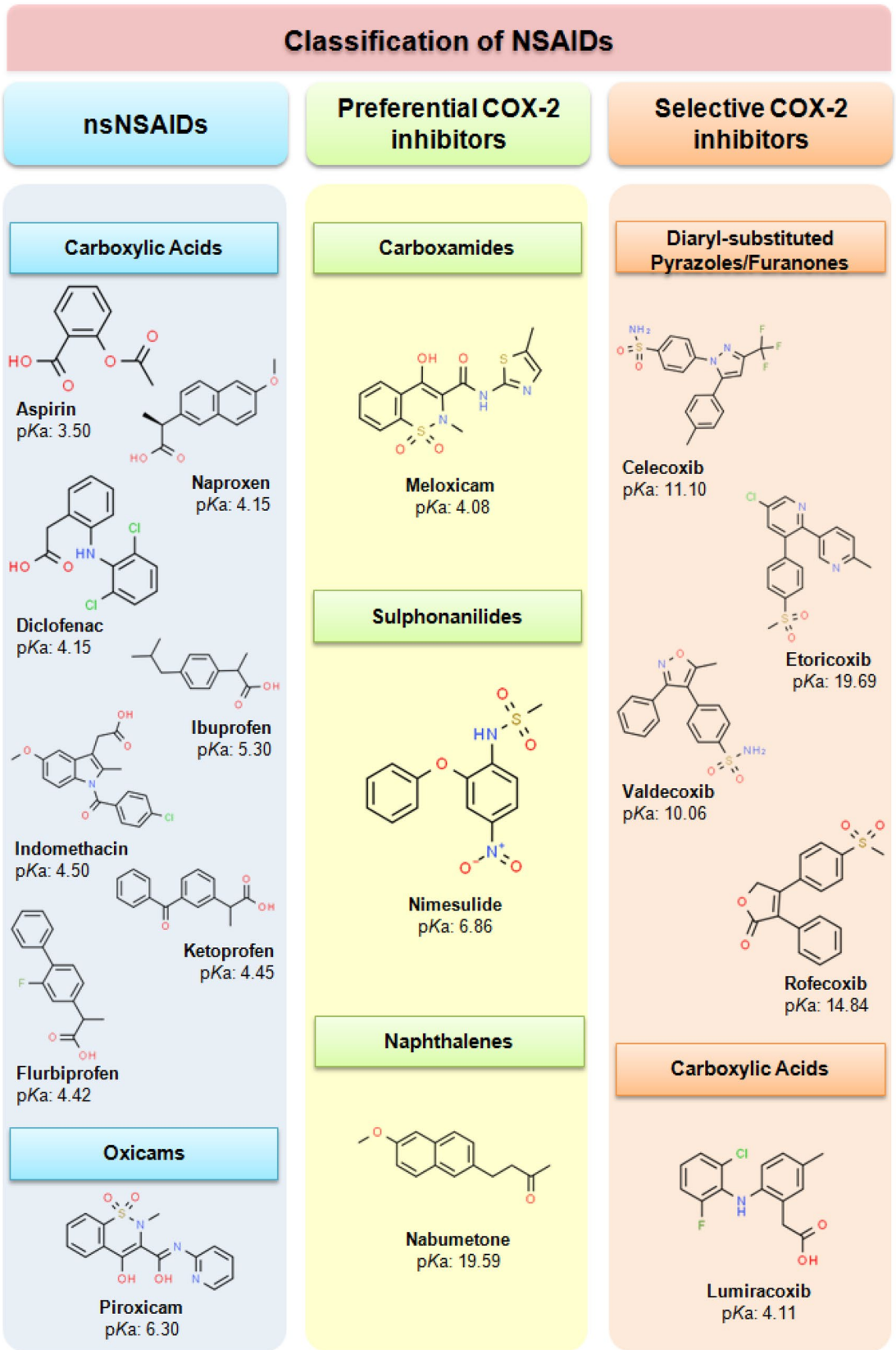

Fig. 4 The classification of NSAIDs regarding their COX inhibitory properties and chemical structures. The experimental or predicted acid dissociation constant (p*K*a) of compounds was obtained from DrugBank

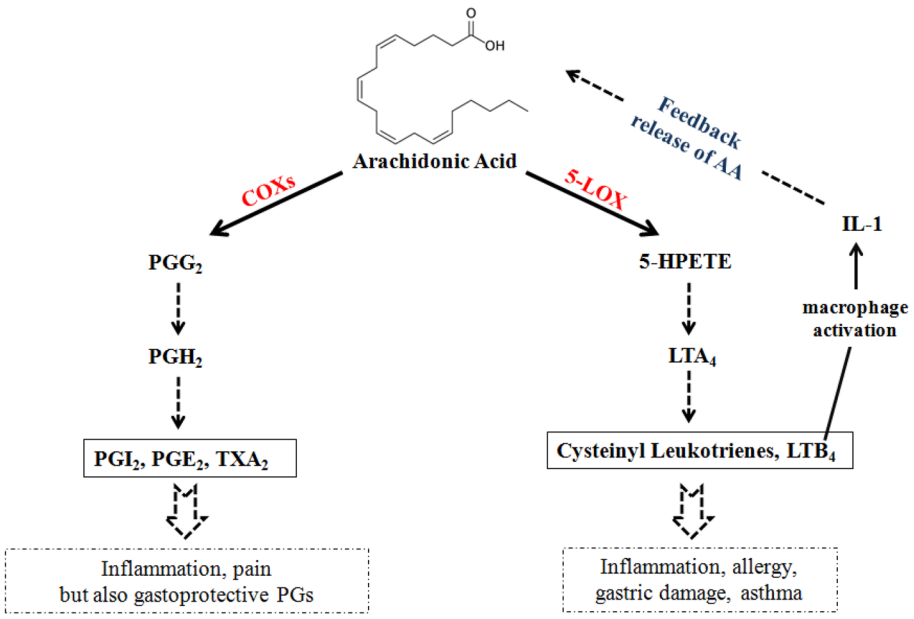

Fig. 5 The possible fates of AA and the connections between COX and LOX pathways

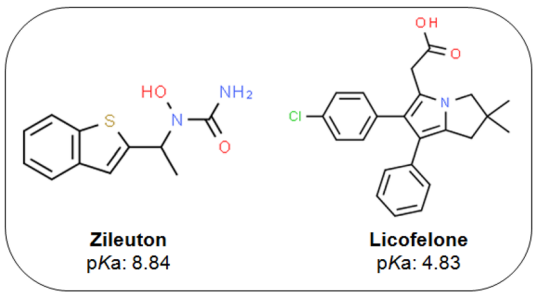

Fig. 6 The chemical structure of zileuton and licofelone. The predicted acid dissociation constant (p*Ka*) of compounds was obtained from DrugBank

into dihydroxy acid leukotriene B_4 (LTB_4), which causes a release of excess ROS and stimulation of the NF-κB pathway (Lee et al. 2007; Okamoto et al. 2010). Additionally, LTB_4 triggers the macrophage activation as well as the expression of IL-1. It is then this cytokine that stimulates the release of AA leading to sustained activation of COX and LOX pathways through a feedback loop as illustrated in Fig. 5. Moreover, the catalysis products of 5-LOX were reported as a risk factor for several inflammatory diseases such as asthma, ulcerative colitis, rhinitis, and even cancer development (Zhao et al. 2012). In the case of COX inhibition by NSAIDs, the 5-LOX pathway is upregulated, thus increasing the possibility for all these adverse effects (Rainsford 1987, 1993; Hudson et al. 1993). Therefore, dual inhibition of COXs and 5-LOX may present a better alternative approach to provide relatively safe NSAIDs.

Development of dual-acting anti-inflammatory drugs (DAAIDs)

Considering the strong pro-inflammatory role associated with LTB_4 and multifactorial properties of cysteinyl-leukotrienes, the inhibition of 5-LOX enzyme was thought to be a promising strategy in the treatment of various inflammatory disorders including asthma, allergic rhinitis, and ulcerative colitis. Zileuton was the first 5-LOX inhibitor marketed in 1996 under the brand name of Zyflo® (Fig. 6). It has been known for its potent selective inhibitory effect on 5-LOX (IC_{50}: 3.7 μM), while sparing the 12-or 15-LOX activities for the production of anti-inflammatory lipoxins (Singh and Pooja 2013). Although Zileuton is still being used to reduce the pathogenesis of asthma at clinics, a variety of adverse effects including hepatic toxicities and extensive drug interactions have been reported. Further studies yielded more potent derivatives with better pharmacokinetics; however, most of them failed in clinical studies due to having serious side effects or insufficient single therapeutic treatment on multifactorial inflammatory diseases.

According to the study conducted by Nickerson and Medvedeff in 1996, the concomitant use of separate inhibitors of leukotriene synthesis, particularly 5-LOX and COX provided a significant amelioration in animal models with arthritis (Nickerson-Nutter and Medvedeff 1996).

This information opened up a new perspective in the design of DAAIDs displaying the mode of action similar to classical NSAIDs while reducing the risk of adverse events (Bertolini et al. 2001; Martel-Pelletier et al. 2003). Currently, various dual COX/5-LOX inhibitors with different pharmacophores can be found in the literature. According to their chemical entities, these can be classified as di

tert-butylphenols, thiophene, pyrazoline, and pyrrolizine derivatives as well as modified forms of FDA-approved NSAIDs (Charlier and Michaux 2003). Among these investigational compounds, licofelone with a structure based on a pyrrole ring linked to two phenyl groups is the only DAAIDs that successfully completed the phase III trial for the treatment of osteoarthritis (Kulkarni and Singh 2007). In animal models, licofelone presented potent anti-inflammatory, analgesic, and antiasthmatic effects with excellent GI and cardiovascular tolerability. Licofelone does not present a selective COX-2 inhibition; however, it is a competitive inhibitor of all three enzymes. The balanced inhibition of both COX enzymes together with 5-LOX inhibition may explain the improved safety profile of the licofelone. In addition to its DAAI properties, licofelone exerts its positive effects on osteoarthritic changes through a multifactorial mechanism of action including the inhibition of MAPK/AP-1 signaling pathways and transcription factor CREB as well as the downregulation of MMP-13.

COX-independent actions: multifactorial role played by NSAIDs

Although inhibition of COX isoforms has been demonstrated as a primary mechanism for the efficacy of the NSAIDs, preclinical and clinical data strongly supported the presence of additional anti-inflammatory properties. Most of these COX-independent mechanisms listed below are NSAID-specific actions that are not reported for all compounds (Fig. 7).

These are in particular:

- *The inhibition of some transcription factors such as activator protein 1 (AP-1) and nuclear factor-kappa B (NF-κB) regulating the expression of various pro-inflammatory cytokines (TNFα, IL-1β, IL6) and mediators (NO, PGE_2, ICAM-1, VCAM-1) as well as enzymes responsible for their productions (iNOS, COX-2)* (Yin et al. 1998; Tegeder et al. 2001; Kim et al. 2004).
- *The inhibition of some signaling pathways involved in inflammatory cascades such as MAPK and PI3K/AKT* (Ou et al. 2007; Bertolotto et al. 2014).
- *Modulation of nuclear receptors such as PPAR-γ and PPAR-δ either acting as agonist or antagonist* (Jarvis et al. 2005).
- *The inhibition of leukocyte and neutrophil adherence (anti-adhesive properties) through interfering with the function of L-selectin and* β2 integrin activation (Díaz-González et al. 1995; García-Vicuña et al. 1997).
- *The inhibition of matrix metalloproteinases particularly MMP2 and MMP9* (Wang et al. 2005; Chi et al. 2009; Zhang et al. 2019).

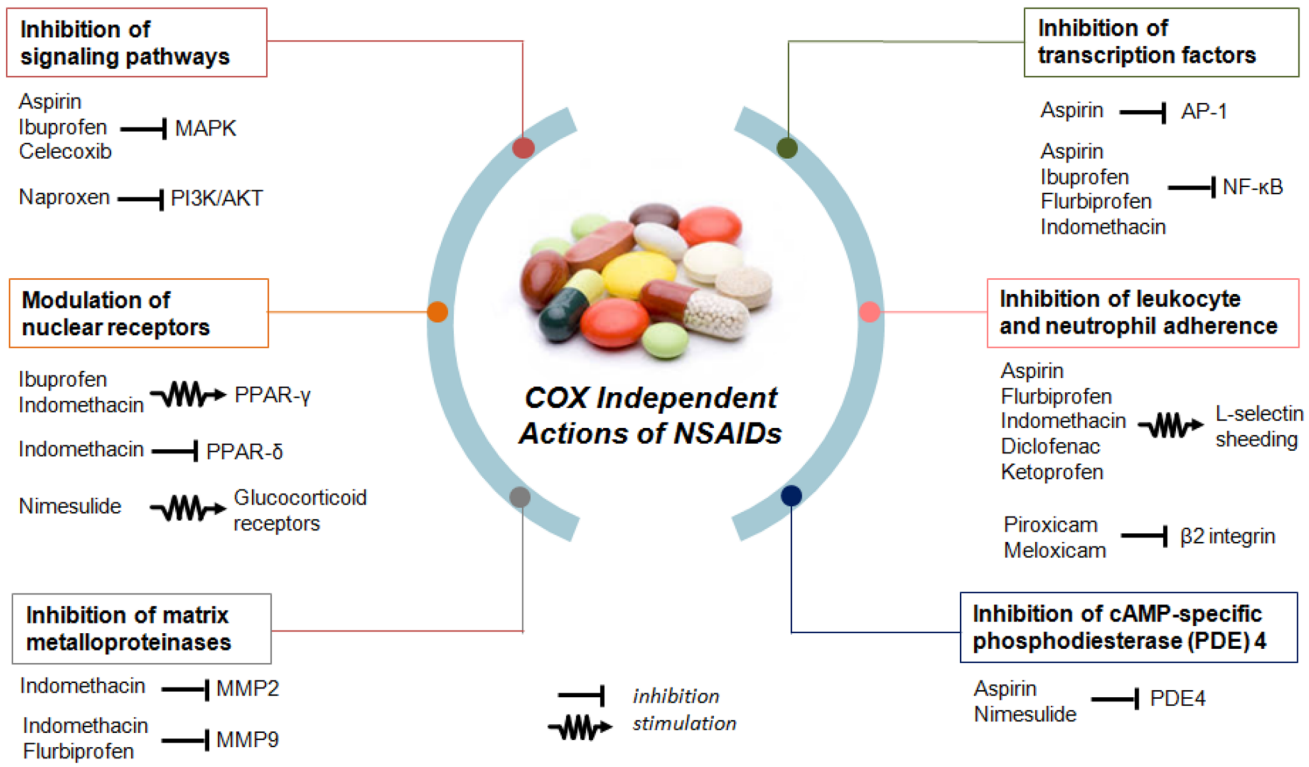

Fig. 7 COX-independent mechanisms of NSAIDs

- *The inhibition of cAMP-specific phosphodiesterase (PDE) IV, a promising therapeutic target for the treatment of chronic pulmonary disorders as well as degenerative and severe neurological diseases. Inhibition of PDE4 by particular NSAIDs may result in elevated intracellular cAMP concentration which in turn regulates inflammatory and immune responses such as suppression of the release of histamine from mast cells and basophils, as well as leukotrienes and cytokines by leukocytes* (Rainsford and Members of the Consensus Report Group on Nimesulide 2006)
- *The activation of glucocorticoid receptors, increased intracellular phosphorylation, and binding of the receptor to the target genes. This action has been addressed specifically for Nimesulide but not for any other NSAIDs, yet.*

Some of these mechanisms of action, which were elucidated through in vitro/in vivo and ex vivo studies, may underlie the antiproliferative, antimetastatic, antiangiogenesis, and neuroprotective effects of particular NSAIDs. The ability of these compounds to modulate different mediators playing a significant role in the degenerative and inflammatory processes confers their potential benefits and brings new ideas to the investigator in the field of drug repurposing.

Repurposing of NSAIDs for cancer chemoprevention and treatment

The polypharmacological profiles of drugs enable researchers to identify and indicate new therapeutic targets, thereby identifying novel therapeutic actions for already approved medicines, which is called drug repurposing. The strategy of drug repurposing, also called re-positioning, re-profiling, and re-tasking is based on the simultaneous interactions of the active molecule with different biomolecules and receptors that may alter the signaling pathways at the same time (Pillaiyar et al. 2020). In addition to clinical observations or experimental data, novel therapeutic roles for old drugs might be suggested by computational methods with systematic and rational approaches to be used against different disease models (Kumar et al. 2019).

It is very well known that researchers approximately spend 13–16 years for a novel molecule to hit the marketing process if everything goes well. During the de novo drug discovery process, 2–3 billion dollars are invested in preclinical studies and clinical trials. In contrast, repurposing strategies save both time and cost to reintroduce the drug with a new purpose by cutting down the time to 1–4 years and budget to 0.3 billion dollars (Dhir et al. 2020). Currently, NSAIDs present promising therapeutic potential in the field of cancer due to their multifactorial effects as mentioned above. In this part of the review, we tried to evaluate major in vitro and in vivo preclinical findings on NSAIDs against cancer. In addition, some of the main findings from clinical trials in oncology have been also examined.

In the early twentieth century, surgery and radiotherapy were the primary methods in the treatment of cancer patients. However, the pioneering studies by the German chemist Paul Ehrlich led to the use of chemicals for the treatment resulting in great success in the history of this multifactorial deadly disease. (Sharifi-Rad et al. 2019). Nowadays, oncologists have diverse options for chemotherapy. However, the genetic background of the cancer patients, the complexity of the diseases, and undesired adverse effects of given drugs lead to limitations on the success rate of treatment. For this reason, the discovery of preventive agents, complementary and alternative therapeutics with reduced side effects, and improved efficacy is still one of the most important challenges in cancer pharmacology.

The NSAIDs have generated great interest in the field of chemoprevention and cancer treatment due to the well-established link between inflammation and tumor microenvironment. There are numerous reports showing the increased levels of *pro-inflammatory cytokines (TNFα, IL-1β, IL6) and mediators (NO, PGE_2, LTB_4)* in several cancer types. They act through multiple cell signaling pathways involved in tumor malignant phenotype maintenance, proliferation, apoptosis, invasion, angiogenesis, and host immune response in the tumorigenesis process (Tian et al. 2020; Nakanishi and Rosenberg 2013; Naldini and Carraro 2005). In this connection, multifactorial properties of NSAIDs mentioned above play important roles against cancer. Moreover, the COX inhibitory action mechanism of NSAIDs is worth mentioning because of the substantially increased expression level of COX-2 in certain cancer tissues (Dempke et al. 2001). For instance, while COX-2 expression could not be observed in normal colorectal tissue, its expression level is detectable in the 85–90% of malignant lesions, thus suggesting a role of COX-2 as a potential biomarker for cancer diagnosis and treatment (Khan and Lee 2011; Roelofs et al. 2014). For this reason, especially coxibs (celecoxib) and preferential COX-2 inhibitors such as nimesulide have been considered as potential candidates in both preventive and therapeutic settings. Moreover, it was shown that the increased expression of COX-2/5-LOX helps epithelial cells for stronger adherence resulting in apoptosis resistant cancer development (Matsuyama et al. 2005). Recently, darbufelon, a candidate dual inhibitor of COX-2/5-LOX, was found as an antiproliferative/invasive agent in colon cancer cells (Che et al. 2016). In these aspects, dual-acting COX-2/5-LOX inhibitors can be considered as promising chemopreventive and therapeutic agents in the future, when they effectively find their places in the markets.

The number of clinical trials investigating the chemopreventive, therapeutic, or complementary effects of aspirin

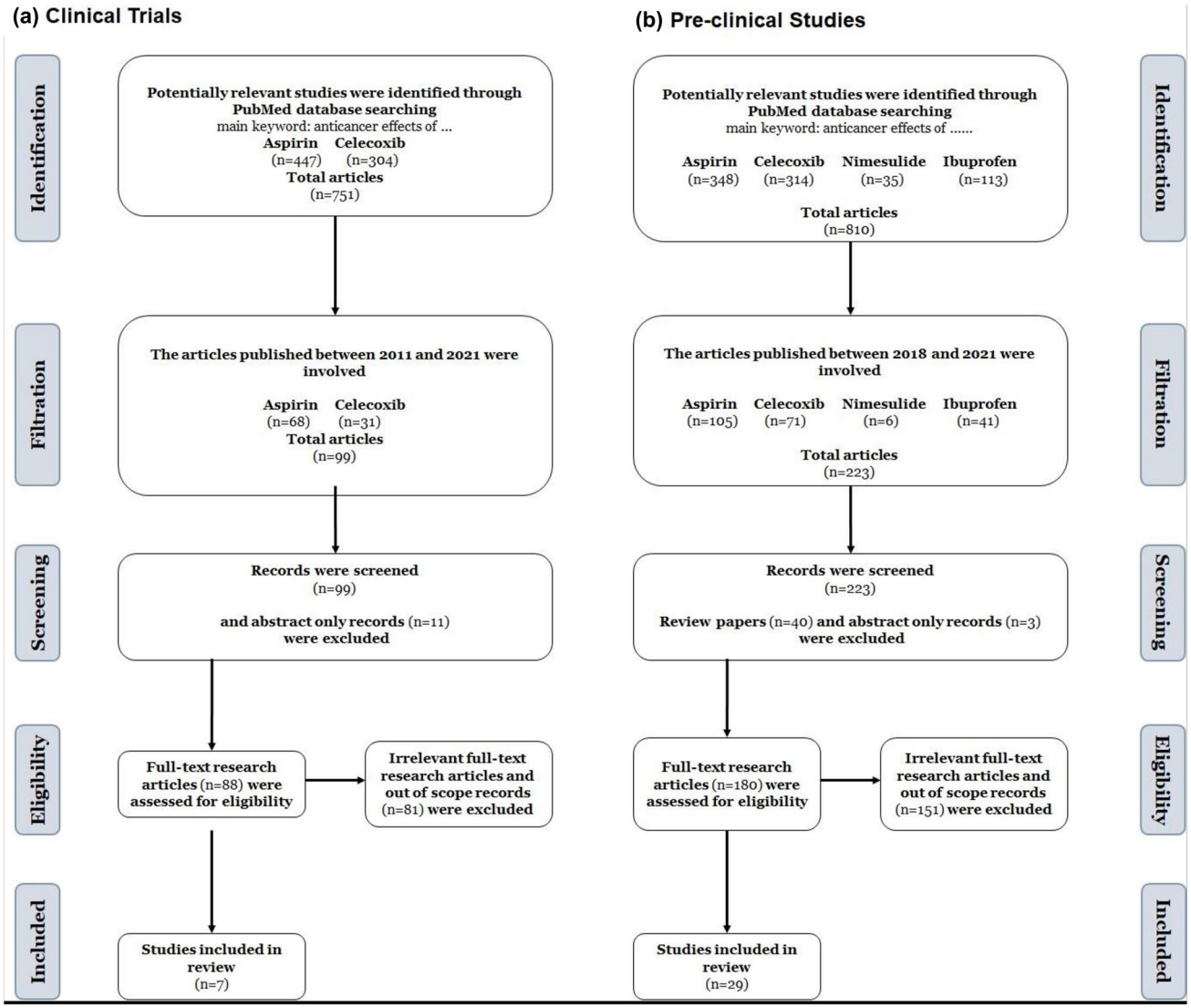

Fig. 8 PRISMA flow diagram showing the search strategy, the number of records identified and the excluded/included articles coming from (**A**) clinical trials and (**B**) preclinical studies

and celecoxib, particularly in cancers associated with the GI tract such as gastric and colorectal carcinoma, are quite high. However, the results from many of them either have not been published or registered yet. Regarding the use of NSAIDs in cancers other than GI-related ones, the vast majority of publications refer to preclinical studies. In the following subsection, we attempted to write a systematic review to bring the potential of NSAID at cancer clinics into view ($n=751$). Initially, clinical studies evaluating the effects of aspirin and celecoxib against colorectal and gastric cancers in the last 10 years were screened and collected from the PubMed® database ($n=99$). Among 99 entries, only 7 studies were relevant, completed and written in English (Fig. 8A). Therefore, they were included and explained in detail for this review.

In the case of non-GI-related cancers instead of clinical studies, which are indeed very limited and lack registered results, we referred to preclinical studies attempting to elucidate effects and modes of action. For the preclinical in vitro and in vivo studies, NSAIDs, especially aspirin, celecoxib, nimesulide, and ibuprofen were screened in the PubMed® database using related keywords, for instance; anticancer effects of aspirin as shown in the PRISMA flow diagram. Due to the large amount of content, the outcomes were filtered and the articles published in English from the year 2018 to 2021 have been collected. Records were screened ($n=223$) and improper studies with different

Table 1 The clinical trials of aspirin and celecoxib in patients with colorectal and gastric cancer

References	Design	Treatment	Patients (*n*)	Study and conclusion
Colon Cancer				
Ishikawa et al.(2012)	Clinical trial randomized double-blind placebo-controlled	Aspirin 100 mg per day Duration: 6–10 months	*n* = 34 patients with familial adenomatous polyposis	The low dose of aspirin intake exhibited a potential for the suppression of colorectal adenoma development or growth in patients with familial adenomatous polyposis
Ishikawa et al. (2021)	Clinical trial randomized double-blind placebo-controlled multicentre	Aspirin 100 mg per day Duration: 8 months	*n* = 104 patients with familial adenomatous polyposis	The low doses of aspirin treatment suppressed the recurrence of colorectal polyps in patients with familial adenomatous polyposis
Thompson et al. (2016)	Clinical trial randomized placebo-controlled	Celecoxib 2 × 200 mg per day Duration:5–23 months	*n* = 824 patients with familial adenomatous polyposis	Limited-duration of celecoxib treatment reduced adenoma recurrence in patients with prior high-risk adenomas
Burn et al. (2020)	Clinical trial randomized double-blind placebo-controlled	Aspirin 600 mg per day Duration: over 2 years	*n* = 861 patients with Lynch syndrome	Adult patients with Lynch syndrome are advised to take 600 mg aspirin daily for at least 2 years to minimize the risk of cancer development
Meyerhardt et al. (2021)	Clinical trial randomized double-blind placebo-controlled	Adjuvant chemotherapy + Celecoxib 400 mg per day Duration: 3 years	*n* = 2526 patients with stage III colon cancer	The addition of celecoxib to the standard adjuvant chemotherapy did not show a significant improvement as compared to the placebo control
Gastric Cancer				
Guo et al. (2017)	Clinical trial randomized case–control multi-center	Adjuvant chemotherapy + Celecoxib 2 × 200 mg per day Duration: 5 months	*n* = 240 patients with advanced gastric cancer	Celecoxib-based first-line chemotherapy was found as an efficacious and safe method for the treatment of gastric cancer
Guo et al. (2019)	Clinical trial randomized case–control multi-center	Adjuvant chemotherapy + Celecoxib 2 × 200 mg per day Duration: 5 months	*n* = 200 patients with metastatic/post-operative recurrent advanced gastric cancer	Celecoxib added as an adjuvant to chemotherapy showed a good clinical application potential in COX-2 positive advanced gastric cancer patients

reasons were excluded. At the final stage, 29 full text research articles were involved in the review (Fig. 8B).

Clinical evidence on the use of NSAIDs against GI-related cancers

Due to correlations between induced COX-2 expression level, inflammatory microenvironment, and aggressive tumor behavior in GI cancers, NSAIDs with COX-2-dependent and -independent actions have been extensively evaluated in clinical trials. In the last decade, particularly aspirin and celecoxib are two prominent drugs under investigation for their chemopreventive and complementary effects in colorectal and gastric cancers. The clinical trials on these drugs have been associated with some promising findings as summarized in Table 1.

Familial adenomatous polyposis (FAP) is a rare condition characterized by adenomatous polyps which may transform into a malignant form of colorectal adenoma, in the large intestine. In a randomized, double-blind, placebo-controlled clinical trial, the effect of aspirin on colorectal adenoma development was screened in 34 patients with FAP. The aspirin administration (100 mg per day) over 6–10 months decreased the diameter, height, and numbers of polyps significantly in subjects as compared to the placebo group (Ishikawa et al. 2013). The same research group also conducted another randomized, double-blind, placebo-controlled, and multicentre clinical trial which involved a higher number of patients with FAP to test the effects of low doses of aspirin treatment, recently. In the study, 104 patients with a history of more than 100 large bowel adenomatous polyps were selected for 8-month trial. These patients were randomly divided into 2 groups as aspirin or aspirin placebo ($n=52$) and mesalazine or mesalazine placebo ($n=52$). The clinical observations proposed that low-doses of aspirin treatment (100 mg/day) could be an alternative method for patients with FAP to reduce the recurrence of colorectal polyps (Ishikawa et al. 2021). In another randomized, placebo-controlled clinical trial, the FAP patients were given 400 mg of celecoxib daily for 5–23 months. According to the data regarding adenoma development, limited-duration of celecoxib treatment reduced adenoma recurrence in patients with prior high-risk adenomas as compared to the placebo-treated group (Thompson et al. 2016).

Lynch syndrome (LS) is a genetic disorder associated with pathogenic mismatch repair gene defect. People with LS have an elevated risk of a wide spectrum of cancers, especially colon cancer. In a randomized double-blind, placebo-controlled clinical trial, the patients with LS were planned a 10-year follow-up to display the role of aspirin use against the development of colon cancer. Accordingly, while the initial data at the early stage of the study suggested no association between aspirin use and colorectal cancer in LS patients (Burn et al. 2011), further data demonstrated these patients taking 600 mg aspirin/day for at least 2 years have significantly reduced risk of cancer development (Burn et al. 2020).

Unlike the aforementioned clinical findings, Meyerhardt et al. (2021) found that celecoxib was not effective on patients with stage III colon cancer. In the double-blind study design, patients were administered 400 mg celecoxib orally per day for 3 years (or until recurrence, death, or unacceptable adverse events) as adjuvant therapy. Patients were subjected to surveillance imaging every 6 months for 6 years. Results indicated that celecoxib did not improve disease-free survival compared with the placebo control group (Meyerhardt et al. 2021).

Apart from the chemopreventive effects of celecoxib in FAP associated-colorectal carcinoma, its effects in the management of gastric cancer were also evaluated by Guo et al. In the randomized, case–control, multi-center clinical trial, patients with advanced gastric cancer were administered celecoxib (2×200 mg per day) combined with chemotherapy for 5 months. The results showed that celecoxib as adjuvant to chemotherapy enhances the scores of overall survival, disease-free survival, progression-free survival, and quality of life in gastric cancer patients with positive COX-2 (Guo et al. 2017). Besides, the same research group also investigated the effects of celecoxib combined with chemotherapy in patients with metastatic/postoperative recurrent advanced gastric cancer. According to the results, they suggest that celecoxib may have potential in clinical application especially for COX-2 positive advanced gastric cancer patients (Guo et al. 2019).

Overall, from the results of all these clinical trials two major findings may be inferred: *First,* the chemopreventive use of NSAIDs in patients with genetic susceptibility to colon carcinoma could be an effective strategy to reduce the risk of development of cancer. *Second,* the coadministration of NSAIDs with chemotherapeutic agents in the treatment of gastric cancer may improve the scores in patients related with survival as well as quality of life. However, further studies with large patient numbers are warranted to fill the gap between mechanism of action studies and clinical evidence.

Preclinical evidences: in vitro and in vivo studies

In the previous section, the repurposing of NSAIDs, particularly aspirin and celecoxib, in the prevention and treatment of colorectal and gastric tumors based on clinical findings of the last ten years were summarized. In the current subsection, we presented the results of in vitro and in vivo studies held in the last four years (2018–2021) for the potential use of NSAIDs in therapy and prevention of other cancer types by focusing on their mode of action (Fig. 9). For this the

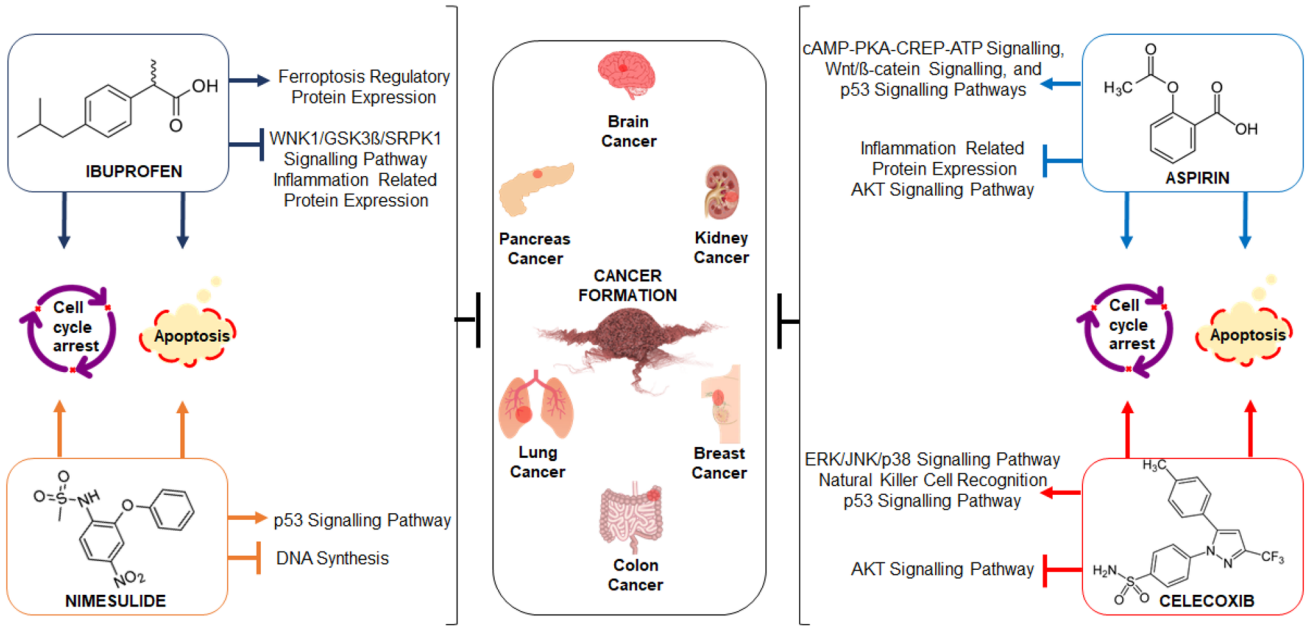

Fig. 9 Reported mode of action of aspirin, celecoxib, nimesulide, and ibuprofen in cancer cells

studies related to the anticancer effects of aspirin, celecoxib, nimesulide and ibuprofen on lung, breast, hepatocarcinoma, melanoma, glioblastoma and pancreatic carcinoma were systematically collected and recruited (Fig. 8B). Besides, the studies presenting evidence for their modulatory roles in cancer stem cells were also included.

Anticancer effects of aspirin

Li et al. (2020) reported that aspirin induced apoptosis by increasing the expression of cleaved PARP and caspase-3 in HCC827 lung and MCF-7 breast cancer cell lines. Expression levels of CD44 and ALDH1A1, cancer stem cell markers, were found to be decreased by aspirin treatment in HCC827GR and HCC827OR lung cancer cell lines. Since the activation of NF-κB is related to cancer in many aspects, aspirin affected NF-κB activity by decreasing phosphorylated NF-κB protein level and nuclear translocation in lung cancer cells (Li et al. 2020). In another study, Der et al. (2020) investigated the metabolic alterations in aspirin-treated and non-treated lewis lung carcinoma implanted C57BL/6 mice models. Aspirin treatment reduced the tumor growth in the high-fat diet-induced obese mice, paralleled by a attenuation in fasting glucose, neutrophil, lymphocytes, p-selectin, TGF-β1, and glutamine levels. In the same study, cell-based analyses also showed that increasing doses of aspirin reduced the cancer cell viability along with long-term clonogenesis while affecting caspase-3 activity minimally (Der et al. 2020). Besides, Zhang et al. (2020a, b) showed that aspirin reduced the protein levels of programmed cell death-ligand 1 (PD-L1) which is expressed in tumor cells and displays an inhibitory role in antitumor immunity in A549 and H1299 human lung cancer cell lines. Further, the promoter of PD-L1 was cloned in a luciferase reporter pGL3-basic plasmid and aspirin was shown to reduce luciferase activity of pGL3-PD-L1. (Zhang et al. 2020b). In the study of Zhang et al. (2020a, b), changes in ALDH + subpopulation were investigated by using ALDH staining in A549 lung, MDA-MB231 breast, and HepG2 hepatocellular cancer cell lines. Aspirin reduced the ALDH + subpopulation along with an increase in apoptosis and a decrease in sphere formation. Aspirin also inhibited inflammation-related stemness gene expression, especially ICAM3 (Zhang et al. 2020a)].

Activation of platelets by mediators released from tumor cells is tightly associated with the progression of metastasis in breast cancer cells through the stimulation of the Akt signaling pathway and interleukin-8 (IL-8) release. Johnson et al. (2019) found that aspirin could inhibit the phosphorylation of Akt pathway signaling proteins such as PDK-1, PTEN, AMPKa and release of IL-8 in thrombin-receptor activating peptide 6 induced cancer cell lines (Johnson et al. 2019). The high expression of an extracellular matrix protein called fibromodulin (FMOD) promotes the migration and invasion capabilities of breast cancer cells. The transcription of FMOD protein is positively regulated by the Wnt/β-Catenin pathway, in which β-Catenin translocates and promotes the FMDO transcription in MDA-MB-231 human breast cancer cells. In the study of Khan et al. (2019), aspirin treatment led to downregulation of the Wnt/β-catenin

pathway-mediated FMDO expression in both mRNA and protein levels by enhancing post-transcriptional modification of β-catenin and its cytoplasmic degradation (Khan et al. 2019).

Moreover, aspirin showed promotion of apoptosis and reduction in colony formation in HepG2 hepatocellular carcinoma cells according to the study of Yuan et al. (2020). Furthermore, the expression levels of Wnt/β-catenin signaling pathway-related proteins were investigated. The treatment of aspirin decreased the translocation of β-catenin and the expression levels of TCF4 and LEF1, which are key molecules of this pathway (Yuan et al. 2020). Another study conducted by Zhang et al. (2021), evaluated the effects of aspirin on different signaling pathways in HepG2 and Hep3b hepatocellular carcinoma cell lines. The outcome of this study indicated that aspirin activates cAMP–PKA–CREB/ATF1 signaling through the AMPK-mediated downregulation of carbamoyl-phosphate synthetase (Zhang et al. 2021).

In the study of Kumar et al. (2018), the effects of aspirin treatment was examined in human melanoma A375 and MTG2 cell lines. The findings indicated that aspirin decreases the cell viability, colony formation and pigmentation through the activation of AMPK and suppression of the synthesis of PGE_2. Further, the studies conducted on human melanoma patient-derived xenografts showed that tumor formation was delayed in the aspirin-treated groups (Kumar et al. 2018).

In the study of Navone et al. (2018) human primary glioblastoma endothelial cells obtained from patients were used as a study model to determine the effects of aspirin on the angiogenesis. The findings showed that aspirin treatment inhibited VEGF secretion and decreased BCL-2 and HIF-2 expressions while increasing the BAX expression at the protein level in these cells. In addition, aspirin inhibited the formation of tube-like structures of glioblastoma cells (Navone et al. 2018).

According to the study of Qorri et al. (2020) aspirin treatment induced early apoptosis in PANC-1 human pancreatic ductal epithelial carcinoma and MiaPaCa-2 human pancreatic carcinoma cell lines through blocking EGF activation of Neu-1, which is responsible for receptor tyrosine kinase activation in cancer cells. In addition, aspirin induced the expression of early apoptotic proteins such as caspase-3 and caspase-7 (Qorri et al. 2020). Moreover, Guo et al. (2021) examined the effects of aspirin treatment in epithelial ovarian cancer cell lines. In this study, aspirin exposure blocks tumor formation, proliferation, and migration through increasing expression of the acetylated and non-acetylated form of the p53 gene both in protein and mRNA levels in the A2780 epithelial ovarian cancer cells. Besides, the expression of p53 target genes such as BAX, FOXF1, PUMA, RRAD were increased at the mRNA level (Guo et al. 2021).

Anticancer effects of celecoxib

The antiproliferative effects of celecoxib and its possible mechanisms of action have been extensively investigated in various cancer cell lines. In the study of Čeponyte et al. (2018), celecoxib showed both antiproliferative and anti clonogenic effects in the BxPC-3 cell line (Čeponytė et al. 2018). Li et al. (2018) identified the differentially expressed genes (DEGs) and differentially expressed long noncoding RNA (DE-LNRs) in the celecoxib-treated human lung squamous cell carcinoma, SK-MES-1. According to the enrichment analyses, 317 DEGs and 25 DE-LNRs were reported to be different between untreated and celecoxib-treated cells. Moreover, 12 cellular pathways regarding mainly Aminoacyl-tRNA biosynthesis, protein processing in the ER, protein export, an amino sugar, nucleotide sugar metabolism, and mammalian target of rapamycin signaling were enriched by the upregulated DEGs. In contrast, downregulated DEGs were enriched in 17 pathways including transforming growth factor signaling pathway, extracellular matrix-receptor interaction, cytokine-cytokine receptor interaction, and p53 signaling pathway with celecoxib treatment. Additionally, protein–protein interaction studies suggested that anticancer effects of celecoxib in cancer cells might be enhanced by a high number of connections between the lncRNAs (lnc-AP000769.1-2:10 and lnc-HFE2-2:1) and the other genes such as VEGFA (vascular endothelial growth factor A), ATF (activating transcription factor)-4, FN1 (fibronectin 1) which play role in the amplification of growth factor for stimulating angiogenesis, anti-tumor effects, and several cellular activities (Li et al. 2018). Increasing the level of natural killer group 2 member D (NKG2D) ligands is tightly linked to the prevention of lung cancer progression. Regarding this, Kim et al. (2020) investigated the effect of celecoxib on the expression level of NKG2D ligands in A549 human lung cancer cells. Study results highlighted that expression level of one of the NKG2D ligands named ULBP-1 was upregulated at both mRNA and protein levels after celecoxib treatment in lung cancer cells. Further, celecoxib enhanced the NK-cell mediated lysis of human lung cancer cells (Kim et al. 2020).

High expression levels of PNO1 (NOB1 homolog) are associated with various types of cancer such as hepatocellular carcinoma. In the study of Dai et al. (2019) celecoxib decreased the tumor formation and migration of Huh-7 hepatocellular carcinoma (HCC) cells through downregulation of PNO1 expression. Further, the study conducted on the hepatocellular carcinoma mouse xenograft model showed that celecoxib was also able to decrease tumor size (Dai et al. 2019). In another study on the rat liver cancer model, Jia et al., (2021) reported that celecoxib delayed tumor formation by altering ERK/JNK/P38 signaling pathway. The protein expression level of p-ERK was decreased, however,

the protein levels of p-JNK and p-p38 were increased with the treatment of celecoxib as compared to the model group (Wang et al. 2021).

Li et al. (2019) demonstrated that celecoxib decreased the viabilities of several cancer cell lines including of F10 murine melanoma, Hela human cervical cancer, A549 human lung cancer, MCF-7 human breast cancer, and 293 T human renal epithelium cancer. Additionally, celecoxib significantly suppressed tumor growth and volume in F10 cells-injected nude mice and decreased the level of PGE_2 in the F10 cell line (Li et al. 2019). In another study conducted by same research team, Ren et al. (2018) revealed that celecoxib also led to a reduction in tumor volume and weight in HeLa-injected BALB/c nude mice as well as decreased PGE_2 release in HeLa cells (human cervix cell line). (Ren et al. 2018). In the study conducted by Iwaniuk et al., the anticancer activity of celecoxib in CAL-27 oral squamous cell carcinoma cells was found to be associated with the stimulated apoptosis and modulated proline metabolism which regulates many biochemical and physiological cellular processes, including carcinogenesis (Tołoczko-Iwaniuk et al. 2020). Another study involving oral squamous cell carcinoma demonstrated that the antiproliferative effect of celecoxib was mediated through reduced expression of ACKR3, CXCL6, and PF4V, as well as by increased expression of genes including CCL28, CMTM1, CMTM3, CMTM4, CXCR6, slit guidance ligand 2, toll-like receptor 2 (TLR2), TLR4, TNFα, and thymidine phosphorylase (TYMP) (Antunes et al. 2019).

Sampson et al. (2019) reported that celecoxib strongly inhibited the efflux of doxorubicin by MRP1 in HEK293 T (human kidney) and H69AR (lung cancer) cell lines (Sampson et al. 2019). In another study, Choi et al. (2021) showed that celecoxib decreased cell viability in the 5-Fluorouracil (5-FU) resistant gastric cancer cell line (AGS FR) by inhibiting the Akt signaling pathway. The protein expression level of PTEN was upregulated, however, the level of p-AKT was suppressed in AGS FR cells upon celecoxib treatment. These studies suggest the potency of celecoxib against drug resistance (Choi et al. 2020). Recently, Watanabe et al., (2020) reported that celecoxib reduced cell proliferation and migration ability of both BICR6 and FaDu head and neck squamous cell carcinoma lines through modulating cognate receptor EP2 to which PGE_2 binds and activate different signaling pathways playing role in cancer development and progression (Watanabe et al. 2020).

Anticancer effects of nimesulide

The study by Chu et al. (2018) showed that nimesulide decreased cell viability and induced early apoptosis in PANC-1 pancreatic cancer cells through Bax/Bcl2 modulation and caspase-3 activation. While the expression of PTEN, which is a lipid phosphatase serving a role in tumor suppression, was augmented by nimesulide; the expression of VEGF was downregulated suggesting a possible suppressive role in angiogenesis (Chu et al. 2018). In the study of Alfaz et al. (2019), nimesulide exhibited an antineoplastic effect on hepatocellular carcinoma via inhibition of DNA synthesis in vitro and in vivo. Nimesulide treatment led to the dilation of blood vessels and the normalization of the levels of several biochemical parameters including serum α-fetoprotein, lipid profile, serum ALP, serum glutamate pyruvate transaminase, and serum glutamate oxaloacetate transaminase in diethylnitrosamine (DENA)-induced Wistar rats. Additionally, nimesulide treatment showed a notable increase in antioxidant enzymes, while decreasing DEPA-induced lipid peroxidation in rat models. Besides, nimesulide decreased cell growth rate and cell viability in BEL-7402 and HepG-2 hepatocellular carcinoma cell lines. [3H] thymidine uptake assay revealed that nimesulide dose-dependently reduced DNA synthesis (Afzal et al. 2019).

Anticancer effects of ibuprofen

Shen et al. (2020) examined the anticancer effects of ibuprofen in several cancer cell lines to understand its action mechanism. Accordingly, percentages of ALDH + subpopulation, side population, and ability of sphere formation were suppressed by ibuprofen treatment in A549 lung cancer cells, MDA-MB-231 breast cancer cells, and HepG2 liver cancer cells. Additionally, the protein expression levels of stemness markers including ALDH1A1 were diminished. Moreover, ibuprofen decreased inflammation-related stemness genes both at the mRNA and protein expression levels in vitro and in vivo while mediating histone 3 (H3) methylation and acetylation to regulate ICAM3 expression (Shen et al. 2020). Gonçalves et al. (2020) reported that ibuprofen leads to a reduction in the expression and activity of oncogenic RAC1B in colorectal cancers. Moreover, ibuprofen treatment in HT29 cancer cell models prevented the phosphorylation and translocation of SRSF1, thereby regulating RAC1B splicing. Since the activities of RAC1B are highly dependent on phosphorylation, which is regulated by GSK3β, they also investigated the inhibitory effects of ibuprofen on GSK3β function. The result showed that ibuprofen did not directly inhibit GSK3β activity; however, ibuprofen provided GSK3β to remain in its inactive form by disrupting the protein–protein interactions of WNK1/GSK3β/SRPK1 protein complex (Gonçalves et al. 2020).

Goa et al., (2020) indicated the anticancer effect of ibuprofen on glioblastoma cells and its molecular mechanism by focusing on ferroptosis, defined as programmed cell death

by iron-dependent lipid peroxidation. Glioblastoma growth was decreased and the survival rate was increased with ibuprofen treatment in U87MG-injected mice. However, the inhibitory effects of ibuprofen on glioblastoma cell viability and lipid peroxidation were restricted when U87MG cells were co-treated with ibuprofen and ferroptosis inhibitors. Furthermore, the expression of Nrf-2, as well as expressions of GPX4 and SLC7A11, key regulatory genes in ferroptosis, were decreased by ibuprofen. These findings suggested that ibuprofen-induced ferroptosis in glioma cells might be mediated by downregulating the Nrf2 signaling pathway (Gao et al. 2020).

All these studies can suggest that NSAIDs may have a supportive role in chemoprevention and cancer treatment especially when they are combined with approved chemotherapeutic agents. However, controlled clinical trials with established outcomes have been urgently needed for their clinical applications as adjuvant therapy.

Concluding remarks

In this review article, we intended to provide a historical perspective on the evolution of NSAIDs, regarding their mode of actions, structural and mechanism-based classifications, adverse effects, multifactorial roles and current situation in drug repurposing. In spite of extensive and long-term efforts to exhibit the therapeutic and preventive effects of NSAIDs in cancer diseases using various preclinical models and clinical trials, none of these molecules or their modified analogs have yet been approved against these conditions. Although there are a substantial number of registered entries for clinical trials evaluating the efficacy and safety of NSAIDs in case of cancer, many of them are in recruiting status. On the other hand, the results of completed studies have not been declared by researchers through scientific papers. One of the most important problems in today's science is not making the obtained results visible, especially when they are not compatible with the expected outcomes. For repurposing of NSAIDs in the field of oncology, more clinical studies which are well designed multicentre, randomized, controlled trials, are warranted.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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