



COX 2-inhibitors; a thorough and updated survey into combinational therapies in cancers

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Received: 11 October 2023 / Accepted: 15 November 2023 / Published online: 2 January 2024
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Abstract

Cyclooxygenase (COX) enzymes are pivotal in inflammation and cancer development. COX-2, in particular, has been implicated in tumor growth, angiogenesis, and immune evasion. Recently, COX-2 inhibitors have arisen as potential therapeutic agents in cancer treatment. In addition, combining COX inhibitors with other treatment modalities has demonstrated the potential to improve therapeutic efficacy. This review aims to investigate the effects of COX inhibition, both alone and in combination with other methods, on signaling pathways and carcinogenesis in various cancers. In this study, a literature search of all major academic databases was conducted (PubMed, Scholar google), including the leading research on the mechanisms of COX-2, COX-2 inhibitors, monotherapy with COX-2 inhibitors, and combining COX-2-inhibitors with chemotherapeutic agents in tumors. The study encompasses preclinical and clinical evidence, highlighting the positive findings and the potential implications for clinical practice. According to preclinical studies, multiple signaling pathways implicated in tumor cell proliferation, survival, invasion, and metastasis can be suppressed by inhibiting COX. In addition, combining COX inhibitors with chemotherapy drugs, targeted therapies, immunotherapies, and miRNA-based approaches has enhanced anti-tumor activity. These results suggest that combination therapy has the potential to overcome resistance mechanisms and improve treatment outcomes. However, caution must be exercised when selecting and administering combination regimens. Not all combinations of COX-2 inhibitors with other drugs result in synergistic effects; some may even have unfavorable interactions. Therefore, personalized approaches that consider the specific characteristics of the cancer and the medications involved are crucial for optimizing therapeutic strategies. In conclusion, as monotherapy or combined with other methods, COX inhibition bears promise in modulating signaling pathways and inhibiting carcinogenesis in various cancers. Additional studies and well-designed clinical trials are required to completely elucidate the efficacy of COX inhibition and combination therapy in enhancing cancer treatment outcomes. This narrative review study provides a detailed summary of COX-2 monotherapy and combination targeted therapy in cancer treatment.

Keywords Cancer · COX-2 · COX-2 inhibitor · Combinational therapy

Abbreviations

COX	Cyclooxygenases	NSAIDs	Non-steroidal anti-inflammatory medications
Ptgs2	Prostaglandin-endoperoxide synthase 2	ICP	Intracranial pressure
PGE2	Prostaglandin E2	TXA2	Thromboxane A2
DMBA	7,12-dimethylbenz[a]anthracene	TRAILR	Tumor necrosis factor-related apoptosis-inducing ligand Receptor
EP1	Prostaglandin E2 receptor 1	IDO	Indoleamine 2,3-dioxygenase
EGFR	Epidermal growth factor receptor	BCL-2	B-cell lymphoma 2
MMPs	Matrix metalloproteinases	OS	Overall survival
TGF2	Transforming growth factor 2	STAT3	Signal transducers and activators of transcription 3
PI3K	Phosphatidylinositol 3-kinase	VEGF	vascular endothelial growth factor
AKT	protein kinase B	JAK-2	Janus Kinase 2
		TKI	Tyrosine kinase inhibitor

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HER2	Human epidermal growth factor receptor 2
NSCLC	Non-small-cell lung cancer
MDSCs	Myeloid-derived suppressor cells
ER	Endoplasmic reticulum
HCC	Hepatocellular carcinoma
miRNA	MicroRNA
ncRNAs	Non-coding RNAs
MDR	Multidrug resistance protein 1
NF- κ B	Nuclear factor kappa B
LRP	low-density lipoprotein receptor-related protein-1
mTOR	Mammalian target of rapamycin
ABCBI	Adenosine triphosphate-binding cassette sub-family B member 1

Introduction

The growing prevalence of cancer across the world poses a risk to human health and well-being and is the second leading cause of death among humans [1]. Cancer can be treated with a variety of medical modalities, including surgery (if the tumors can be removed surgically), chemotherapy, radiation therapy, targeted therapy, and immunotherapy. Combining many therapeutic modalities into a single treatment plan is standard practice. For instance, the most typical form of combination treatment consists of surgery, local radiation, and systemic and local chemotherapy. However, due to chemoresistance, reduced radiation sensitivity, and other tumor molecular adaptations, the results of therapy are frequently poor and troublesome, which can result in a high risk of recurrence of cancer [2].

Prostaglandins are produced from arachidonic acid, and cyclooxygenases (COX) are the rate-limiting enzymes in this process. There are now two isozymes, namely COX-1 and COX-2 [3]. While COX-1 expression is constant in most healthy tissues, COX-2 expression can be induced and is frequently elevated in inflammatory and many neoplastic tissues [4]. Since COX-2 appears to be involved in multiple steps of the carcinogenesis process, blocking its activity has been shown to have anti-tumor and anti-angiogenic effects in a wide range of human malignancies [3].

Since COX-2 signaling pathways exist, using COX-2 inhibitors as a therapeutic method for treating human malignancies appears appealing. This new information might make it much easier to combine COX-2 inhibitor therapy with other types of cancer treatment in future research [5]. A medication combination like this one can simultaneously target several molecular targets. This study analyzed and detailed recent advancements in COX-2 inhibitors in combination with other anti-cancer medications because it has been discovered that COX-2 inhibitors produce anti-tumor activity and have extensive effects on human malignancies.

COX-2 inhibition was previously thought to target tumors primarily by inhibiting the COX-2 pathway. However, the anti-tumor effects of Celecoxib may also occur through mechanisms unrelated to COX-2. For example, studies have shown that COX-2 inhibitors can promote apoptosis and reduce cell proliferation and angiogenesis in cancer cells by regulating various signaling pathways in cancer. In addition, studies have shown that COX-2 inhibitors increase the sensitivity of cancer cells to chemotherapy and radiation therapy [6]. However, they are treated with antibiotics, traditional medicine, etc. It was recently established. Therefore, this review describes investigations into the mechanisms by which COX-2 inhibitors intervene in cancer through different signaling pathways and examines in vitro and in vivo studies to investigate how COX-2 inhibition enhances COX-2-independent mechanisms. in the clinical treatment of cancer [5, 7]. This study provides a detailed summary of COX-2 monotherapy and combination therapy with targeted therapy in cancer treatment.

COX-2 role in tumors

Carcinogen activation

Prostaglandin H synthase metabolizes numerous compounds when metabolizing arachidonic acid. Chemical metabolism often produces reactive metabolites with mutagenic and carcinogenic properties. COX peroxidase converts procarcinogens to carcinogens and causes tumors. COX peroxidase activity co-oxidizes several xenobiotics into mutagens. Cytochrome P-450s in the liver catalyze these oxidative processes, preventing mutagens. However, the colon contains low numbers of P-450s and other monooxygenases; thus, COX peroxidase activity co-oxidizes many xenobiotics to mutagens [8, 9]. This activity may also affect tobacco-exposed organs like the lung, oral cavity, and bladder. COX's peroxidase activity activates procarcinogens like benzo[a]pyrene to intracellular electrophiles. Arachidonic acid metabolism generates mutagens. Malondialdehyde, a highly reactive byproduct of arachidonic acid oxidation, forms DNA adducts [10].

COX enzymes can activate a variety of environmental and dietary carcinogens, suggesting a role in the activation pathway of aromatic and heterocyclic amines and polycyclic hydrocarbons at extra-hepatic sites during early or late carcinogenesis.

Cancer development and progression

Liu et al. [11] initially reported COX-2 overexpression-induced cancer. They placed the murine COX-2 gene, Prostaglandin-endoperoxide synthase 2 (P_{ts}2), downstream of

a murine mammary tumor virus promoter. Thus, mammary gland hyperplasia and cancer were linked to significant COX-2 expression in epithelial cells and elevated Prostaglandin E2 (PGE2). Only this study has shown that COX-2 initiates tumors. However, mice models of skin carcinogenesis have been created employing the *Ptgs2* gene downstream of the K5 or K14 promoters. Depending on COX-2 expression and prostaglandin accumulation, transgenic mice lines with keratin 5 promoter-driven COX-2 overexpression in basal epidermal cells have preneoplastic skin. Transgenics developed skin cancers after one treatment with 7,12-dimethylbenz[*a*]anthracene (DMBA). Transgenic mice did not need long-term treatment with the tumor promoter phorbol 12-myristate 13-acetate (PMA, a protein kinase C activator). COX-2 overexpression does not induce tumors but sensitizes the epidermis to genotoxic chemicals. Thus, COX-2 promotes tumor growth, not initiation [12].

In colorectal tumor models, COX-2 promotes tumors. In APC Δ 716 mice crossed with mice with an inactivated *Ptgs2* gene, Oshima et al. [40] found a reduction in colonic polyps. The number of large polyps was significantly reduced. Homozygous mice were more affected. Oshima et al. [13] tested COX-2 gene (*Ptgs2*) knockouts and a new COX-2 inhibitor on APC Δ 716 knockout mice, a model of human familial adenomatous polyposis, to establish COX-2's role in colorectal carcinogenesis. *Ptgs2* null mutations significantly reduced intestinal polyps. Selective COX-2 inhibitors reduced polyp number in APC Δ 716 mice more than sulindac, inhibiting COX-1 and COX-2. These findings suggest that COX-2-selective inhibitors may effectively treat colorectal polyposis and cancer. Downstream pathways also implicate COX-2 in carcinogenesis. Cells that overexpress COX-2 have higher concentrations of PGE2, which is thought to be the most significant COX-2 downstream effector. Homozygous deletion of EP2, a cell-surface receptor of PGE2, reduces intestinal polyps in APC Δ 716 mice. Homozygous gene deletion for additional PGE2 receptors, Prostaglandin E2 receptor 1 (EP1) or EP3, did not impact intestinal polyp growth in APC Δ 716 mice [14]. PGE2 promotes tumor angiogenesis, invasion, and metastasis. PGE2 expression causes several COX-2 actions. Only COX-2-expressing colon cancer cells establish colonies after PGE2 exposure [15].

Since EGFR is regarded as a therapeutic target for cancer treatment and several Epidermal growth factor receptor (EGFR) inhibitors have been discovered, activation of EGFR via PGE2 is of great interest [16]. Therefore, their interaction with COX-2 inhibitors may represent a novel development in cancer treatment. PGE2 and EGFR pathways frequently cooperate to cause or accelerate tumor development and block apoptosis. For instance, by activating the PI3kinase/Akt pathway, PGE2 prevents apoptosis. The exact biochemical mechanism is stimulated by EGFR

receptor activation [17]. The EGFR and COX-2 pathways interact with one another. PGE2 directly causes EGFR transactivation by inducing the Src pathway and stimulating EGFR signaling by shedding active EGFR ligands from the plasma membrane [18, 19]. On the other hand, EGFR transactivation promotes COX-2 expression and, consequently, PGE2 expression via AP-1-mediated induction, creating a feedback loop of stimulation [17].

Invasion and Metastasis

The sneakiest and most lethal features of cancer are invasion and metastasis. Cell mobility and matrix breakdown are crucial to this process. An enzyme family that breaks down the matrix includes matrix metalloproteinases (MMPs) [20]. Their expression is linked to blood vessel penetration, metastasis, and tumor cell invasion of the basement membrane and stroma. Human colon cancer cells (Caco-2) were irreversibly transfected with either a COX-2 expression vector or a vector without the COX-2 insert in research to assess the impact of COX-2 on metastasis. Compared to the original Caco-2 cells or the control cells that had been transfected with a vector, the Caco-2 cells that constitutively produced COX-2 gained greater invasiveness. Metalloproteinase-2 activation was one of the biochemical modifications connected to this phenotypic shift [21].

Furthermore, Fernandez et al. reported that COX-2 inhibition reduced MMP-2 and MMP-9 release in the human prostate carcinoma cell line DU-145 [22]. Rat intestinal epithelial (RIE) cells permanently transfected with a COX-2 expression vector orientated in the sense (RIE-S) or antisense (RIE-AS) direction were utilized to determine a correlation between changes in the adhesion characteristics of cancer cells and COX-2 over-expression. The extracellular matrix (ECM) proteins were more readily adhered to by the RIE-S cells, which also produced more significant amounts of COX-2 protein. However, RIE-AS cells had higher levels of E-cadherin than RIE-S cells did. Increased Bcl2 expression, decreased Transforming growth factor 2 (TGF2) receptor levels, and resistance to butyrate-induced apoptosis were all seen in RIE-S cells [23]. These results show intestinal epithelial cells overexpressing COX-2 undergo phenotypic alterations that may increase their tumorigenic potential. Cancer cells are more likely to adhere to endothelial cells when COX-2 is expressed [24]. Selective COX-2 inhibitors have been used to stop animal metastasis, consistent with these in vitro results [25, 26]. For instance, COX-2-specific drugs block the ability of the highly metastatic NCI-H460-LNM35 cell line to spread when it is transplanted into SCID mice (severe combined immunodeficiency) [27].

COX-2 signaling

COX-2 signaling refers to the molecular pathways and processes that involve the COX-2 enzyme. COX-2 is an inducible enzyme that plays a significant role in inflammation and pain by catalyzing the conversion of arachidonic acid to prostaglandins and other bioactive lipids (26). While COX-2 is expressed at low levels constitutively in some tissues, its expression is rapidly up-regulated in response to inflammatory stimuli, growth factors, and cytokines (27).

Multiple cell types, including immune, endothelial, and tumor cells, exhibit tightly regulated activation of COX-2 signaling. PGE₂, a byproduct of COX-2 activity, contributes to inflammation, angiogenesis, immune modulation, cell proliferation, and survival (26). Abnormal COX-2 signaling has been linked to tumor development, progression, and metastasis in the context of cancer (26). Numerous cancer varieties, including colorectal, breast, lung, prostate, and gastric cancers, have been observed to exhibit elevated COX-2 expression. Overexpression of COX-2 is linked to increased tumor growth, apoptosis resistance, enhanced angiogenesis, and immune evasion (27).

COX-2 signaling intersects with several crucial cancer biological pathways. For instance, prostaglandins derived from COX-2 can activate the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway, promoting cell survival and proliferation [28]. Additionally, they can modulate the Wnt/-catenin pathway, resulting in increased tumor growth and invasion [29]. In addition, COX-2 signaling can affect the tumor microenvironment by modulating the secretion of cytokines, chemokines, and growth factors, which can promote immune suppression, tumor-associated angiogenesis, and extracellular matrix remodeling [30]. Given the function of COX-2 signaling in cancer, targeting this pathway has emerged as a potential therapeutic strategy. COX-2 inhibitors, such as non-steroidal anti-inflammatory medications (NSAIDs) and selective COX-2 inhibitors, have been developed and extensively investigated. These inhibitors block the enzymatic activity of COX-2, reducing the production of prostaglandins and modulating downstream signaling events [31].

Multiple anti-cancer effects have been linked to the inhibition of COX-2 signaling, including the suppression of tumor cell proliferation, induction of apoptosis, inhibition of angiogenesis, and modulation of the immune system (28). COX-2 inhibitors have demonstrated efficacy as monotherapy or combined with other cancer therapies. In the prevention and treatment of colorectal cancer, their use has been linked to reduced polyp formation and enhanced survival rates [32]. COX-2 inhibitors can modulate the tumor microenvironment in addition to their direct effects

on tumor cells. These inhibitors create a less favorable environment for tumor growth and metastasis by diminishing inflammation, angiogenesis, and immunosuppression. In addition, the combination of COX-2 inhibitors with other therapeutic agents, such as chemotherapy, targeted therapies, immunotherapies, and small RNA-based approaches, has shown synergistic effects and improved treatment outcomes [33, 34].

Overall, COX-2 signaling is essential to cancer biology, and targeting this pathway with COX-2 inhibitors is a promising therapeutic strategy. There is a need for additional research to elucidate the precise mechanisms of COX-2 signaling in various cancer types, identify predictive biomarkers of response, and optimize the use of COX-2 inhibitors in combination therapies. Understanding COX-2 signaling and its role in cancer can create more effective and individualized treatment methods to improve patient outcomes and quality of life [35].

Types of COX-2 inhibitors

COX-2 inhibitors, particularly selective ones, represent a promising class of drugs with the potential to revolutionize cancer treatment. These inhibitors offer a new generation of medications that can be used as adjunct therapies for cancer, providing higher efficacy and fewer side effects compared to traditional treatments. The development of selective COX-2 inhibitors has captivated the interest of scientists due to their remarkable attributes [3, 36].

However, drug resistance poses a significant challenge in cancer therapy, and overcoming it is crucial for successful treatment. Various factors contribute to drug resistance, including the activity of p-glycoprotein (p-gp) and other mechanisms. Therefore, it is imperative to develop newer drugs that exhibit a reduced incidence of drug resistance [3].

Specific selective COX-2 inhibitors, like Celecoxib and Caldecocixib, contain a primary sulfonamide moiety in their chemical structures. This sulfonamide, located in the para position of the phenyl ring attached to the central scaffold of these molecules, not only exerts a COX-2 inhibitory effect but also possesses carbonic anhydrase (CA, EC 4.2.1.1) inhibitory activity. The primary sulfonamide binds to a zinc ion at the active site of the CA enzyme, leading to the inhibition of cancer-related human CA IX isoform at nanomolar concentrations. The anti-cancer effects of these compounds may be attributed to the inhibition of carbonic anhydrase, specifically targeting isoforms IX and XII, in addition to the selective inhibition of COX-2 [37–39].

Acetazolamide, a primary sulfonamide compound, is a classic CA inhibitor used to treat conditions such as glaucoma and elevated intracranial pressure (ICP) [40]. Studies have indicated that acetazolamide could impede the growth

of intestinal polyps in mice, suggesting the involvement of CA in the intestinal carcinogenesis process [41].

Carbonic anhydrase, a well-known zinc metalloprotein, catalyzes the reaction between carbon dioxide and water to produce bicarbonate anion (HCO_3^-). Solid tumors often exhibit a hypoxic environment with acidic cytoplasmic pH. Cancer cells employ specific compensatory mechanisms, including the overexpression of CA isoform IX, to survive under such unfavorable conditions. CA activity helps maintain favorable physiological conditions within tumor cells by alkalizing the acidic pH. Overexpression of CA also promotes tumor cell invasion and metastasis [42].

CA inhibition can be considered a novel anti-cancer treatment strategy since unbuffered acidic conditions in the cell cytoplasm ultimately lead to cell death. Additionally, it has been discovered that COX-1 inhibition may play a role in preventing tumorigenesis, indicating that it is not solely COX-2 involved in this process. Thus, non-selective COX inhibitors also exhibit potential as candidates for cancer prevention [43].

Despite the therapeutic benefits of selective COX-2 inhibitors in cancer and inflammation, their widespread use has been associated with adverse effects on various tissues, including the liver, kidney, and cardiovascular system. These inhibitors have been linked to myocardial infarction, hypertension, and diminished renal blood flow [44]. The exact origin of cardiac side effects, such as those observed with rofecoxib, resulting from COX-2 selectivity remains unclear [45]. It is postulated that the cardiovascular adverse effects of selective COX-2 inhibitors arise from an imbalance between thromboxane A₂ (TXA₂) derived from COX-1, acting as a thrombotic agent, and prostacyclin (PGI₂), a vasoprotective factor derived from COX-2. The dosage and duration of treatment may influence the cardiovascular toxicity of these drugs [31].

Moreover, the unique chemical structure, pharmacokinetic profile, and production of toxic metabolites from rofecoxib may contribute to its cardiac toxicity [45]. Research suggests that both NSAIDs and COX-2 inhibitors are associated with an increased risk of gastrointestinal, renal, and cardiovascular adverse reactions [46]. Furthermore, COX-2 inhibitors have been found to induce mitochondrial toxicity by inhibiting oxidative phosphorylation in rat liver tissue mitochondria [47].

However, the potential for these side effects can be mitigated by utilizing novel drug delivery systems such as nanospheres, nanogels, microemulsions, microparticles, liposomes, monoclonal antibodies, and other advanced drug administration approaches. These innovative methods offer a way to enhance drug targeting, reduce systemic toxicity, and improve the overall safety profile of COX-2 inhibitors [48].

In conclusion, selective COX-2 inhibitors hold great promise as a new generation of drugs for cancer therapy.

Their ability to inhibit COX-2 and carbonic anhydrase, particularly isoforms IX and XII, makes them potential candidates for effective anti-cancer treatment. However, drug resistance and the adverse effects of COX-2 inhibitors emphasize the need for continued research and development to enhance their efficacy, reduce side effects, and explore novel drug delivery systems.

Monotherapy with COX-2 inhibitors

In the treatment of cancer, monotherapy with COX-2 inhibitors has attracted considerable interest as a potential therapeutic approach. COX-2 inhibitors are a class of drugs that selectively inhibit the enzyme COX-2, which is implicated in inflammation and tumorigenesis. By targeting COX-2, these inhibitors provide a unique opportunity to modulate pathways associated with cancer progression, making them potential candidates for use as stand-alone therapies [49]. COX-2 inhibitors' mechanisms of action involve their ability to inhibit COX-2, resulting in decreased prostaglandin production selectively. Prostaglandins perform crucial roles in tumor development, angiogenesis, and immune regulation. In addition, it has been demonstrated that COX-2 inhibitors induce apoptosis in cancer cells, inhibit cell proliferation, and modulate the signaling pathways involved in inflammation and cell survival [50].

Numerous cancer varieties, including colorectal, breast, lung, and prostate cancer, have been the subject of clinical studies examining the efficacy of COX-2 inhibitors as monotherapy [51–54]. While some studies have demonstrated promising results regarding decreased tumor growth, enhanced survival rates, and improved patient outcomes, the findings have not been consistent across all studies [55]. Variations in response to COX-2 inhibitor monotherapy have been observed across patient populations, highlighting the need for additional research to identify specific subgroups of patients most likely to benefit from this treatment strategy [56].

Monotherapy with COX-2 inhibitors presents several obstacles. These include determining the optimal dose and duration of treatment, managing potential adverse effects, and devising predictive biomarkers to identify patients who will respond positively to treatment. Ongoing research focuses on addressing these obstacles and optimizing the effectiveness of COX-2 inhibitor monotherapy. Combining COX-2 inhibitors with other targeted therapies or chemotherapy is being investigated to improve treatment outcomes [57].

Regarding the monotherapy with COX-2 inhibitors, Celecoxib monotherapy enhanced apoptosis in hepatocellular carcinoma by inducing the expression of CD95, tumor necrosis factor-related apoptosis-inducing ligands 1 and 2 (TRAILR1 and R2). It also promotes the expression of

myeloid leukemia-1, an anti-apoptotic member of the Bcl-2 family, leading to increased tumor cell apoptosis [58]. Breast cancer experiments have shown that COX-2 inhibition with Celecoxib can significantly reduce Indoleamine 2,3-dioxygenase (IDO) levels in breast cancer, and PGE2 regulation downstream of COX-2 can also inhibit the tryptophan-consuming process of IDO [59]. Valdecoxib is a U.S.-approved non-steroidal anti-inflammatory drug. Food and Drug Administration (FDA) for the treatment of inflammatory diseases. However, it was recently reported that the anti-tumor effect of Valdecoxib induces cell proliferation and apoptosis in nasopharyngeal cancer cells and lung cancer cells. A recent study has shown that Valdecoxib monotherapy significantly reduces cell migration and proliferation and induces apoptosis in hypopharyngeal squamous cell carcinoma cells by regulating the PI3K signaling pathway [60]. Nanoparticle-loaded Etoricoxib exhibited significant cytotoxicity against lung cancer cells by inducing apoptosis/necrosis and cell cycle arrest in lung cancer cells *in vitro* [61].

In conclusion, monotherapy with COX-2 inhibitors is an effective cancer treatment option. The selective targeting of COX-2 and its associated pathways has potential as a stand-alone treatment for certain types of cancer despite the heterogeneity of the clinical evidence and the need for additional research. Understanding the mechanisms of action, refining treatment strategies, and undertaking well-designed clinical trials will help realize the full potential of COX-2 inhibitors as cancer monotherapy.

COX-2 inhibitors plus conventional chemotherapy

Combining COX-2 inhibitors with chemotherapy medications has been investigated as a potential method for enhancing the efficacy of cancer treatment. Chemotherapy employs a variety of medicines with distinct mechanisms of action to target and eliminate cancer cells. However, standard chemotherapy frequently results in the enrichment or induction of cancer stem cells, which can cause chemoresistance and cancer recurrence [62].

Chemotherapy is associated with severe side effects. To address these issues, researchers have investigated the combination of COX-2 inhibitors with various chemotherapy drugs, such as biological alkylating agents, anti-tumor antibiotics, and anti-tumor plant-derived medicines. The objective is to increase the efficacy of chemotherapy while decreasing its adverse effects [63].

Combination with biological alkylating agents: In chemotherapy, biological alkylating agents such as Cyclophosphamide, Temozolomide, Cisplatin, Oxaliplatin, and so on are frequently employed [64]. However, they can produce toxicity in healthy tissues. Researchers have coupled COX-2 inhibitors, such as Celecoxib, with alkylating agents to

mitigate these side effects. Studies have revealed encouraging results, such as decreased toxicity, enhanced anti-tumor activity, and patient tolerability [5]. For instance, a combination of Cyclophosphamide and Celecoxib demonstrated efficacy and low toxicity in metastatic breast cancer patients [65]. Similarly, combining Celecoxib and Temozolomide improved survival rates and quality of life in malignant glioma patients [66]. The combination of Celecoxib with Cisplatin and Gefitinib increased the lethal effect of chemotherapy drugs on cancer cells. It reduced the multidrug resistance response by inhibiting COX-2 and anti-apoptotic B-cell lymphoma 2 (Bcl-2) gene expression [67]. Tolfenamic acid is a non-steroidal anti-inflammatory drug and selective COX-2 inhibitor; its combination with Cisplatin has recently been shown to enhance apoptosis in breast cancer by increasing P-53 levels [68].

Combination with antimetabolites: 5-FU combination with Celecoxib reduced Squamous cell carcinoma proliferation by alleviating the AKT pathway [69]. 5-FU combination with Celecoxib has been shown to be associated with decreased progression-free survival (PFS) and overall survival (OS) of HCC [70]. Capecitabine, an Oxaliplatin combination with Celecoxib, reduced renal cancer through inducing apoptosis and alleviating neovascularization [71].

Combination with anti-tumor antibiotics: Anti-tumor antibiotics such as doxorubicin and epirubicin are frequently used in chemotherapy for cancer [72]. They can, however, have dose-dependent adverse effects on the heart. Combining COX-2 inhibitors, such as Celecoxib, with these antibiotics has demonstrated promise in inhibiting the progression of hepatocellular carcinoma (HCC) and enhancing cytotoxic activity [73]. It has also been discovered that combination therapy suppresses hepatic cancer stem cells, inhibits tumor cell proliferation and angiogenesis, and stimulates anti-tumor immunity. Significantly, the combination therapy did not exacerbate the myelotoxicity induced by antibiotics [73]. Combining Doxorubicin and Celecoxib reduced cell proliferation in non-small lung cancer [74] and induced apoptosis in human skin cancer [75] and breast cancer [26, 33].

Combination with plant anti-tumor drugs: Anti-tumor pharmaceuticals derived from plants, such as Curcumin, Vinblastine, Vincristine, and Paclitaxel, have been studied with COX-2 inhibitors. These combinations have demonstrated synergistic anti-cancer effects in numerous cancer types. For instance, Curcumin and Celecoxib have synergistic effects against colon, pancreatic, and hepatocellular carcinomas [76–78]. The combinations have inhibited tumor proliferation, angiogenesis, and inflammatory factors [78]. Combining Plumbagin and Celecoxib reduced cell proliferation in melanoma by modulating the signal transducers and activators of transcription 3 (STAT3) signaling pathway [79]. Combining Tetrahydrocurcumin and Celecoxib inhibited cell angiogenesis by down-regulating the vascular

endothelial growth factor (VEGF) and decreased tumor growth by alleviating EGFR in cervical cancer [80]. Utilizing nanotechnology-based delivery systems has improved the delivery and release of these medications to tumor tissues, thereby increasing their effectiveness. It is worth noting that not all combinations of COX-2 inhibitors with chemotherapy drugs result in increased anti-tumor activity. Some varieties may not show synergistic effects or may even have unfavorable interactions. Therefore, caution is required when selecting and administering these combination regimens, considering the specific characteristics of the cancer and the drugs involved [81].

Overall, combining COX-2 inhibitors with chemotherapy drugs can improve cancer treatment outcomes by increasing efficacy, minimizing side effects, and overcoming chemoresistance. Additional research and clinical trials are necessary to completely comprehend the optimal combinations, dosages, and treatment protocols for particular types of cancer.

COX-2 inhibitors plus radiotherapy

In the context of radiotherapy, COX-2 inhibitors have demonstrated promise for improving the efficacy of radiation treatment in multiple ways:

Overcoming radioresistance: Radioresistance is the capacity of cancer cells to sustain radiation exposure and continue to increase. It can reduce the effectiveness of radiotherapy. By targeting specific signaling pathways implicated in radioresistance, COX-2 inhibitors have been found to sensitize cancer cells to radiation therapy (61). For instance, they can inhibit the Janus Kinase 2 (JAK-2)/STAT3 signaling pathway, which promotes cell survival and radiation resistance. COX-2 inhibitors can make cancer cells more susceptible to the detrimental effects of radiation by interfering with these pathways [82].

Enhancing tumor response: It has been demonstrated that COX-2 inhibitors strengthen the response of tumors to radiation therapy. They can inhibit tumor growth by inhibiting cell proliferation and fostering apoptosis in cancer cells [83]. In addition, COX-2 inhibitors can reduce the expression of aggressive tumor-associated markers, such as VEGF and MMPs. These effects improve the therapeutic efficacy of radiation treatment [84].

Protecting normal tissues: One of the difficulties of radiation therapy is the potential for harm to healthy adjacent tissues. It has been discovered that COX-2 inhibitors have a protective effect on normal cells by reducing radiation-induced inflammation and toxicity. They can aid in preserving the integrity and function of normal tissues, thereby minimizing treatment-related adverse effects and enhancing patient outcomes overall [85].

In various varieties of cancer, including lung cancer, head and neck cancer, colorectal cancer, and prostate cancer,

the combination of COX-2 inhibitors with radiotherapy is currently being investigated. COX-2 inhibitors combined with radiotherapy have shown promising results in pre-clinical models and early-phase clinical trials, demonstrating enhanced tumor control and better treatment outcomes [86–89].

However, it is essential to be aware that COX-2 inhibitors can have adverse effects, including hazards to the cardiovascular system and issues with the digestive system, mainly when used for an extended period or in specific patient populations. Because of this, these products' usage should be considered cautiously, and medical specialists should properly supervise patients [90].

In conclusion, COX-2 inhibitors have emerged as potentially useful adjuvant therapies in cancer treatment. They are intriguing candidates for combination therapy strategies because they can circumvent radioresistance, boost tumor response, and protect normal tissues. However, additional research is required to maximize their use, identify the patient populations that would benefit the most from the treatment, discover the most effective dosage and treatment regimens, and address potential adverse effects. COX-2 inhibitors play an important part in cancer treatment; therefore, discussing this topic with a medical expert is essential for making individualized and well-informed decisions on how best to use them.

COX-2 inhibitors plus kinase inhibitors

To date, tyrosine kinase inhibitor (TKI) therapy has successfully controlled several human cancers, including estrogen receptor, progesterone receptor, and/or human epidermal growth factor receptor 2 (HER2)-positive breast cancer and non-small-cell lung cancer (NSCLC). Therefore, combination therapy may help improve drug sensitivity, and previous studies have shown that combining COX-2 inhibitors with EGFR TKIs can prevent colonic adenoma in mice due to their effects on these two signaling pathways [91].

COX-2-dependent signaling represents a potential mechanism of clinical resistance to EGFR-TKI treatment. A phase 2 clinical trial confirmed the toxicity of Erlotinib and Celecoxib for treating patients with advanced NSCLC [92]. The efficacy of Erlotinib plus Celecoxib was assessed in patients with advanced NSCLC with wild-type EGFR and determined the improved efficacy and toxicity of the therapy [93]. Another study conducted by Sun et al. showed that the combination of erlotinib and Celecoxib increased radiosensitivity after radiotherapy by blocking EGFR- and COX-2-related pathways and inducing apoptosis through the PI3K/AKT signaling pathway [94]. Another study found that Gefitinib (EGFR-TKI) and celecoxib induced apoptosis in EGFR-mutant NSCLC cell lines [94]. In this regard, Lin et al. revealed the efficacy of combining Gefitinib and

Celecoxib in prostate cancer by improving tumor cell death and overcoming docetaxel resistance [95].

Vandetanib is a potent VEGFR-2 inhibitor that inhibits tumor growth and prolongs survival. Vandetanib and Celecoxib combination therapy was first reported to have a powerful anti-tumor effect on osteosarcoma *in vivo* and *in vitro* by inducing ERK phosphorylation [96]. Kaya et al. demonstrated that combining Motesanib and DuP-697 (selective COX-2 inhibitor) significantly induced apoptosis and attenuated angiogenesis in CRC cells [97]. Celecoxib and Imatinib enhanced anti-tumor activity through caspase-3 activation in CML [98]. Zhao et al. reported that the combination of Sunitinib and Celecoxib exhibited potent anti-tumor activity in renal cell carcinoma cells by significantly reducing the expression of GM-CSF and STAT3 and attenuating the levels of myeloid-derived suppressor cells (MDSCs) [99]. The combination of Sorafenib and Meloxicam (selective COX-2 inhibitor) induced apoptosis by activating endoplasmic reticulum (ER) stress in hepatocellular carcinoma (HCC) [100]. Combination therapy of Celecoxib with Sorafenib and/or sildenafil has been shown to potently induce apoptosis by significantly reducing the expression of multiple chaperone proteins in ovarian cancer. Their combination sensitized ovarian cancer cells to platinum therapy [101].

COX-2 inhibitors plus angiogenesis inhibitors

Drugs known as angiogenesis inhibitors can thwart the angiogenesis process, also known as developing new blood vessels. This process is essential for the growth and spread of tumors because it forms new blood vessels, which provide cancer cells with nutrition and oxygen. These medications try to reduce the blood supply to tumors by preventing angiogenesis; this will starve the tumors and lead to slow down or even hinder tumor growth [102]. When COX-2 inhibitors and angiogenesis inhibitors are combined, several synergistic effects are possible:

- A) Anti-inflammatory and anti-angiogenic effects: Inflammation promotes angiogenesis, and COX-2 inhibitors reduce inflammation. These drugs can reduce the production of inflammatory molecules that contribute to angiogenesis by inhibiting COX-2. When combined with angiogenesis inhibitors, COX-2 inhibitors reduce inflammation and angiogenesis, thereby potentially enhancing the suppression of tumor growth and metastasis [26].
- B) Complementary mechanisms of action: COX-2 and angiogenesis inhibitors inhibit cancer progression via distinct mechanisms. Angiogenesis inhibitors target specific molecules implicated in angiogenesis, such as VEGF and its receptors, whereas COX-2 inhibitors primarily target the COX-2 enzyme and associated signal-

ing pathways. The purpose of combining these medications is to attain additive or synergistic effects; this means they can simultaneously target multiple ways, addressing various aspects of tumor development and potentially resulting in improved therapeutic outcomes [103].

- C) Overcoming resistance: Over time, tumors can develop resistance to single-agent therapies, diminishing treatment efficacy; this resistance can be circumvented by combining COX-2 and angiogenesis inhibitors. COX-2 inhibitors can sensitize resistant tumor cells to angiogenesis inhibitors' effects, thereby enhancing angiogenesis inhibitors' efficacy in resistant tumors. This strategy aims to attack the cancer from numerous angles, increasing the likelihood of a successful treatment response [104].
- D) Improved treatment response: COX-2 inhibitors have improved the efficacy of radiation therapy, a standard cancer treatment modality. COX-2 inhibitors may augment the effectiveness of radiation treatment with angiogenesis inhibitors since COX-2 inhibitors can target both tumor cells and tumor vasculature, potentially enhancing tumor control and overall treatment efficacy [105].

Notably, the clinical benefits of combining COX-2 and angiogenesis inhibitors are still being evaluated, and additional research is necessary. The optimal scheduling, dosage, and sequencing of these medications and criteria for patient selection are being investigated. Additionally, it is essential to consider potential adverse effects and drug interactions that may arise when using combination therapies, as they may differ from those of individual drugs [106].

Ongoing clinical trials investigate the combination of COX-2 inhibitors and angiogenesis inhibitors in various cancer types, including colorectal cancer, lung cancer, and breast cancer. These studies aim to determine this combination therapy's efficacy, safety, and optimal application. Patients can receive the most up-to-date information and treatment options regarding COX-2 and angiogenesis inhibitors for cancer by consulting with a healthcare professional and contemplating participation in clinical trials [107, 108].

COX-2 inhibitors plus other small inhibitors

miRNAs (microRNAs) and non-coding RNAs (ncRNAs) are small RNA molecules that significantly regulate genes. They regulate gene expression, and their dysregulation has been linked to numerous diseases, including malignancy. Certain microRNAs and non-coding RNAs can function as oncogenes or tumor suppressors in cancer [109].

Combining COX-2 inhibitors with miRNA or ncRNA inhibitors can have several potential benefits:

- A) Synergistic effects on cancer pathways: microRNAs and non-coding RNAs regulate diverse cancer-related routes, including cell proliferation, apoptosis, angiogenesis, and metastasis. By targeting these molecules, it may be possible to improve the effectiveness of COX-2 inhibitors on these pathways. The combination therapy aims to produce a synergistic effect, resulting in enhanced inhibition of tumor growth and dissemination [110].
- B) Overcoming treatment resistance: Resistance to single-agent cancer treatments can be a significant obstacle. Combining COX-2 inhibitors with inhibitors of microRNA or non-coding RNA may assist in overcoming this resistance. Combining therapy can potentially enhance the therapeutic response by simultaneously targeting multiple molecular pathways by addressing various mechanisms contributing to treatment resistance [111].
- C) Modulation of immune response: microRNAs and non-coding RNAs affect the immune response in the tumor microenvironment. Some microRNAs have been related to immune evasion by tumors [112], whereas others have been linked to immune activation and anti-tumor immune responses [113]. Targeting specific miRNAs or ncRNAs may be possible to modulate the immune response and boost the efficacy of immune-based therapies, such as immunotherapy or checkpoint inhibitors, when administered with COX-2 inhibitors [114].
- D) Personalized medicine approach: As potential biomarkers for cancer diagnosis, prognosis, and treatment response prediction, miRNAs and ncRNAs have dem-

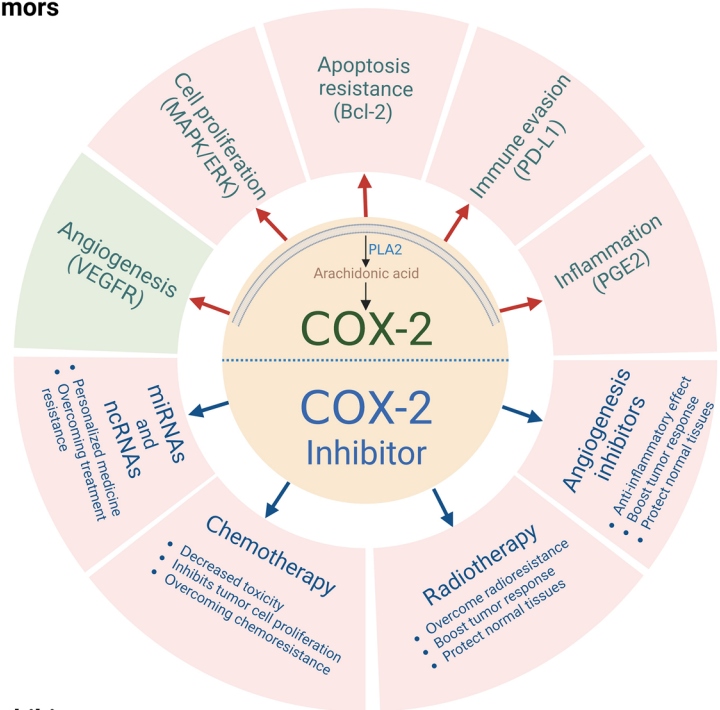
onstrated promise [115]. Integrating the analysis of these molecules with COX-2 inhibitors can facilitate the customization of patient-specific treatment strategies. Identifying specific miRNAs or ncRNAs that are dysregulated in a patient’s cancer makes it possible to devise personalized therapies that target these particular molecules and pathways [116].

Notably, the miRNA and ncRNA research field is still evolving, and the therapeutic potential of these molecules is still being investigated. In clinical trials, the combination of COX-2 inhibitors with miRNA or ncRNA inhibitors for the treatment of colorectal cancer, breast cancer, and lung cancer, among others, is being investigated. These studies aim to determine these combination therapies’ efficacy, safety, and optimal application [117–119].

In conclusion, combining COX-2 inhibitors with miRNA or ncRNA inhibitors bears promise as a cancer treatment strategy for enhancing the therapeutic effects of COX-2 inhibition. By simultaneously targeting multiple molecular pathways and overcoming treatment resistance, this strategy seeks to improve patient outcomes. However, additional research is necessary to comprehend these combinations’ mechanisms and clinical benefits thoroughly. Patients can obtain the most up-to-date information and personalized treatment options by consulting with health-care professionals and contemplating participation in clinical trials (Fig. 1).

Fig. 1 Types of COX-2 inhibitors and a schematic of the role of its inhibition in cancer therapy

COX2 role in tumors



Types of COX2 inhibitors

Discussion and conclusion

Combination therapy with COX-2 inhibitors is a promising strategy to improve the efficacy of cancer treatment. Extensive preclinical and clinical evidence supports the hypothesis that combining COX-2 inhibitors with other drugs can induce synergistic effects, overcome drug resistance, modulate the tumor microenvironment, and revolutionize personalized medicine. Combining COX-2 inhibitors with miRNAs, ncRNAs, angiogenesis inhibitors, immunotherapy, and conventional chemotherapy agents improved anti-tumor activity compared with monotherapy. This combination enhances treatment response and

extends disease control by targeting pathways involved in tumor growth, angiogenesis, immune evasion, and drug resistance. Combination therapies have the potential to address the complexity and heterogeneity of cancer by capitalizing on the unique mechanisms of action of COX-2 inhibitors and their ability to modulate diverse molecular and cellular processes [120, 121].

Combination therapy has the potential to overcome drug resistance, which is a significant advantage. Combination therapies can bypass the adaptive mechanisms used by cancer cells, thereby avoiding treatments that target multiple signaling pathways and cellular processes. This strategy represents a significant change in cancer treatment and offers a new treatment option for patients

Table 1 Combination of COX-2 inhibitors in the treatment of human cancers

Combination	Cancer type	Effect(s)	Mechanism/Signaling pathway	References
Celecoxib and cyclophosphamide	Breast cancer	Anti-angiogenic	Decrease VEGF	[126]
Celecoxib and 5-FU	Squamous cell carcinoma	Inhibit proliferation	Inhibit AKT pathway	[69]
Celecoxib and epirubicin	Novikoff hepatoma	Reduce proliferating	Suppress CD44, CD133 and MDR-1 expression	[127]
Celecoxib and doxorubicin	Human skin cancer	Enhance apoptosis	Inhibit AKT pathway	[75]
Celecoxib and rapamycin	Gastric cancer	Increase sensitivity	Inhibit PI3K/AKT pathway	[128]
Celecoxib and doxorubicin	Drug-resistant breast cancer	Induce apoptosis	Inhibit P-gp expression	[26]
Celecoxib and curcumin	HCC	Inhibit angiogenesis	Inhibit Akt, NF- κ B, and PGE2	[129]
Celecoxib and cisplatin	Nasopharyngeal carcinoma	Induce apoptosis	Decreasing LRP gene expression	[130]
Tolfenamic acid and cisplatin	Breast cancer	Induce apoptosis	Increasing P-53	[68]
Celecoxib and erlotinib	NSLC	Enhance apoptosis and radiosensitivity	Inhibit EGFR and PI3K/AKT pathway	[94]
Celecoxib and gefitinib	NSLC	Induce apoptosis	Inhibit EGFR pathway	[131]
Celecoxib and gefitinib	Prostate cancer	Enhance apoptosis/reduce tumor proliferation	Increased caspase 3 cleavage/ decreases in BCL-2 and ABCB1 expression	[132]
Celecoxib and vandetanib	Osteosarcoma	Promote apoptosis	Inducing ERK phosphorylation	[96]
Celecoxib and imatinib	Colon cancer	Inhibit proliferation	Increase Caspase-3 activity	[98]
Celecoxib and imatinib	Chronic myelogenous leukemia	Induce apoptosis	AMPK activating/ mTORC inhibition	[133]
Celecoxib and sunitinib	Renal cancer	Immunomodulation/ Alleviate tumor progress	Inhibit GM-CSF and STAT3 expression/Alleviating MDSCs	[134]
Meloxicam and sorafenib	HCC	Induce apoptosis	Activate ER stress	[135]
Celecoxib and sorafenib	Ovarian cancer	Induce apoptosis/	Reduce chaperone proteins	[135]
Celecoxib and sildenafil	Ovarian cancer	Induce apoptosis/Increased platinum sensitivity	Reduce chaperone proteins	[135]
DuP-697 and motesanib	Colorectal cancer	Induce angiogenesis and apoptosis	–	[97]
Celecoxib and 5-FU	Hepatocellular carcinoma	Increased overall survival (OS)	–	[136]
Celecoxib and capecitabine	Renal cancer	Induce apoptosis	–	[137]
Celecoxib and oxaliplatin	Renal cancer	Induce apoptosis	–	[137]
Celecoxib and doxorubicin	NSLC	Reduced cell proliferation	–	[75]
Celecoxib and doxorubicin	Breast cancer	Reduced cell proliferation	–	[33]

resistant to existing treatments. In addition, combination therapy with COX-2 inhibitors could modify the tumor microenvironment, thereby improving the immune environment. By reducing immunosuppression and increasing anti-tumor immune responses, these combinations may enhance the efficacy of immunotherapy and pave the way for new immunomodulatory approaches. The tumor microenvironment plays a critical role in tumor progression and treatment response, and combination therapies target this dynamic ecosystem, providing a comprehensive approach to cancer treatment [122, 123].

Clinicians can tailor treatment regimens to individual patients by identifying specific molecular targets, biomarkers, and patient characteristics, maximizing treatment efficacy and minimizing side effects. Identifying patients most likely to benefit from combination therapy will improve treatment outcomes, optimize resource allocation, and reduce treatment-related toxicities. However, it must be recognized that the safety and tolerability of combination therapy must be carefully evaluated. However, the safety profile of COX-2 inhibitors is well established, and their combination with other drugs was generally well tolerated in early clinical trials. Monitoring and managing potential side effects and drug interactions is essential to ensure patient safety and optimize treatment outcomes. Combination therapy with COX-2 inhibitors has the potential to improve cancer outcomes significantly. Multifaceted strategies involving microRNAs, noncoding RNAs, angiogenesis inhibitors, immunotherapy, and conventional chemotherapy agents provide a comprehensive blueprint to address the complex biology of cancer. Potential impacts of combination therapy include increased anti-tumor activity, elimination of drug resistance, modification of the tumor microenvironment, personalized drug delivery approaches, and favorable safety profile [124, 125].

In conclusion, although preclinical and early clinical trial results are promising, further studies are needed to confirm these findings and determine the functionality of COX-2 inhibitor combination therapies in routine clinical practice. Large-scale clinical trials, comprehensive biomarker studies, and in-depth mechanistic studies are needed to fully understand the therapeutic potential and optimize the use of COX-2 inhibitors in combination with other modalities. By harnessing the power of combination therapies, we can improve patient outcomes, extend survival, and ultimately move closer to a future where cancer is easier to manage and treat; however, further studies are needed to determine the exact role of COX as well as its corresponding pathways and its hindering in cancer (Table 1).

Acknowledgements The authors extend their appreciation to the Dean-ship of Scientific Research at King Khalid University for funding this

work through a large group Research Project under grant number RGP2/420/44.

Author Contribution PR, HB, YFM, HRAKA-H, ATA: Conceptualization, Writing—original draft preparation. MMD, MMA-T, RSZ, AA: Conceptualization, Writing—review and editing, Visualization. AH: Conceptualization, Supervision. All authors read and approved the final manuscript.

Funding This study was supported by the deanship of Scientific Research at King Khalid University for funding this work through a large group Research Project under grant number RGP2/420/44.

Data availability Data sharing does not apply to this article as no new data were created or analyzed in this review study.

Declarations

Competing interests None.

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