International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)
IJAMSCR |Vol.12 | Issue 3| Jul - Sep -2024
www.ijamscr.com
DOI : https://doi.org/10.61096/ijamscr.v12.iss3.2024.293-300
ISSN: 2347-6567

Review

Exploring Novel Cancer Targets Unveiled By Established Nsaids

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Published on: 12 Jul 2024

Published by:
DrSriram Publications

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs), particularly selective inhibitors of cyclooxygenase-2 (COX-2), have emerged as promising candidates for their potential to combat cancer. Epidemiological, clinical, and preclinical investigations have consistently demonstrated their association with a reduced incidence of various cancers, including colorectal, lung, esophageal, pancreatic, cervical, skin, and ovarian cancers. However, the clinical application of traditional NSAIDs is hindered by gastrointestinal adverse effects. Selective COX-2 inhibitors offer improved gastrointestinal profiles, sparking interest in their role as chemopreventive agents. Yet, uncertainties persist regarding whether the anticancer effects of NSAIDs solely stem from COX inhibition or involve COX-independent mechanisms.

This review aims to delineate the anticancer mechanisms of NSAIDs, focusing on aspirin and similar agents, while exploring avenues for enhancement. Mechanistic insights suggest potential targets beyond COX enzymes, such as phosphodiesterase-5 (PDE5) inhibition, leading to apoptosis induction. Additionally, advancements in medicinal chemistry propose novel strategies, including aspirin prodrugs, nitroaspirin, NF-κB inhibitors, and modified sulindac derivatives, for targeted cancer therapy. Furthermore, 2-arylpropionic acid-derived NSAIDs have demonstrated antiproliferative effects across various cancer cell lines, highlighting their potential as lead compounds for potent and safe anticancer agents.

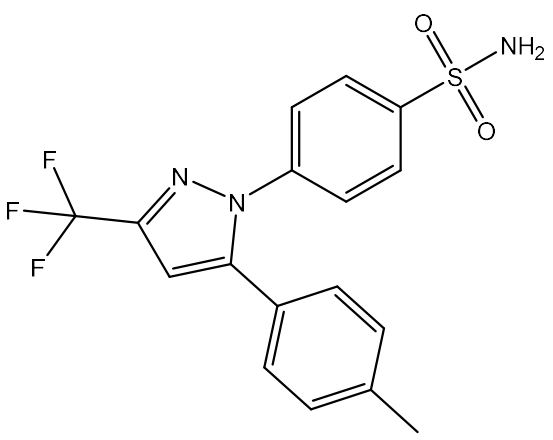
Despite these advancements, further research is warranted to elucidate precise mechanisms of action, optimize treatment regimens, and evaluate risk-benefit ratios. By advancing our understanding of NSAIDs in cancer prevention and treatment, we can potentially revolutionize cancer care paradigms.

Keywords: Selective COX-2 Inhibitors, Cancer Prevention, Chemoprevention, Aspirin.

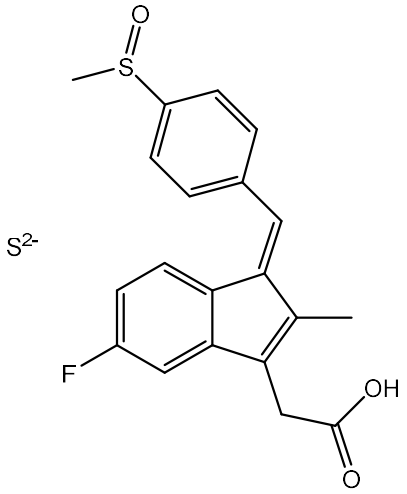
INTRODUCTION

Epidemiological, clinical, and preclinical investigations present strong indications that NSAIDs, such as COX-2 selective inhibitors, exhibit anticancer characteristics [1]. Initial hypotheses suggested that anti-inflammatory medications might eliminate inflammatory agents within the tumor's surrounding microenvironment, facilitating direct exposure of tumor cells to immune cells. Subsequently, immune cells could act via immune recognition to eliminate tumor cells [2]. Consistent use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) is linked to reduced occurrences of specific cancers marked by inflammation, notably colorectal cancer, as well as lung, esophageal, pancreatic, cervical, skin, and ovarian cancers [3,4,5]. Preventing cancer through chemotherapy requires a delicate equilibrium, weighing the potential advantages against the possible adverse effects on individuals who may have stayed healthy even without the treatment [6]. Considering that the lifetime risk of developing colorectal cancer is just over 5%, the yearly likelihood of an individual developing colon cancer is notably lower. Hence, chemopreventive treatments for healthy individuals should have minimal side effects. However, the gastrointestinal side effects associated with traditional NSAIDs limit their prolonged use. The introduction of selective COX-2 inhibitors, which offer better gastrointestinal profiles compared to NSAIDs, presents new avenues for cancer prevention. However, it remains uncertain whether all the anticancer benefits associated with traditional NSAIDs stem solely from their ability to inhibit cyclooxygenases. This review seeks to distinguish the anticancer effects of aspirin and similar NSAIDs and explore potential opportunities for enhancement [7].

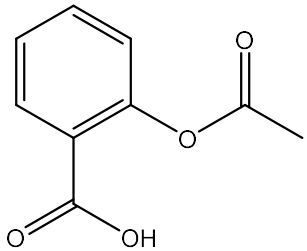
Some non-steroidal anti-inflammatory drugs (NSAIDs) have been studied for their anti-cancer properties.



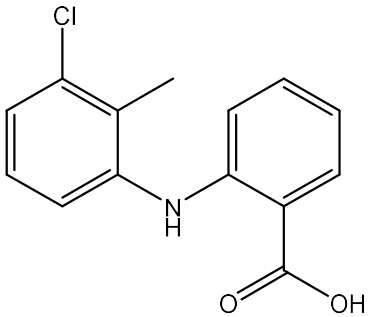
Celecoxib



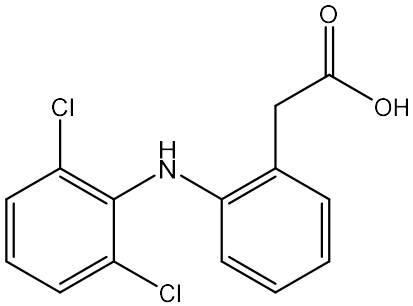
Sulindac sulfide



Aspirin



Tolfenamic acid



Diclofenac

COX and Cancer

Since 1983, when researchers initially noticed the colon adenoma-reducing antiproliferative effect of sulindac [8]. Significant endeavors have been dedicated to assessing the anticancer capabilities of NSAIDs. Numerous studies have explored the involvement of COX enzymes in cancer development. The elevated levels of COX-2 found in various tumor types have substantiated this perspective [9, 10, 11]. COX-2 inhibitors might also enhance or combine effectively with anticancer medications, either synergistically or additively, for cancer prevention or treatment purposes [12]. These reports suggest that the mechanism by which NSAIDs exhibit anticancer activity may be facilitated through one of the following means.

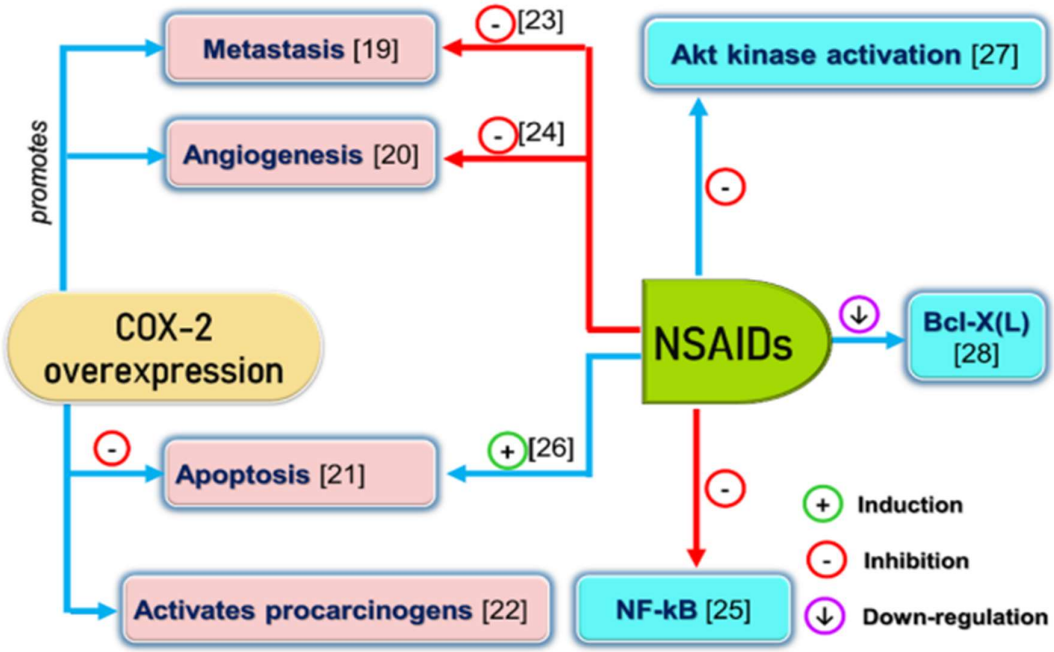


Fig 1: The impact of COX-2 over expression and NSAIDs on various targets or processes implicated in cancer [13].

"Exploring Fresh Anticancer Avenues with Established NSAIDs"

It's estimated that around 28 million individuals in the US are affected by sporadic colonic adenomas. About 10% of these cases exhibit high lesion formation rates and could benefit from a safe and effective chemopreventive medication, ideally used alongside colonoscopy to hinder new lesion formation and decrease the overall risk of disease progression. While NSAIDs have demonstrated promise in experimental, clinical, and epidemiological investigations, their potential is hindered by gastrointestinal, renal, and cardiovascular side effects stemming from cyclooxygenase-1 and/or -2 suppression and prostaglandin depletion. Mechanistic analyses propose that their anticancer effects might involve COX-independent or off-target actions, potentially through PDE5 inhibition and subsequent cGMP elevation, leading to apoptosis induction. Hence, there's potential in developing safer and more effective chemopreventive drugs by targeting PDE5. Nonetheless, further research is needed to clarify the precise role of this isozyme and the cGMP pathway in tumorigenesis. [14].

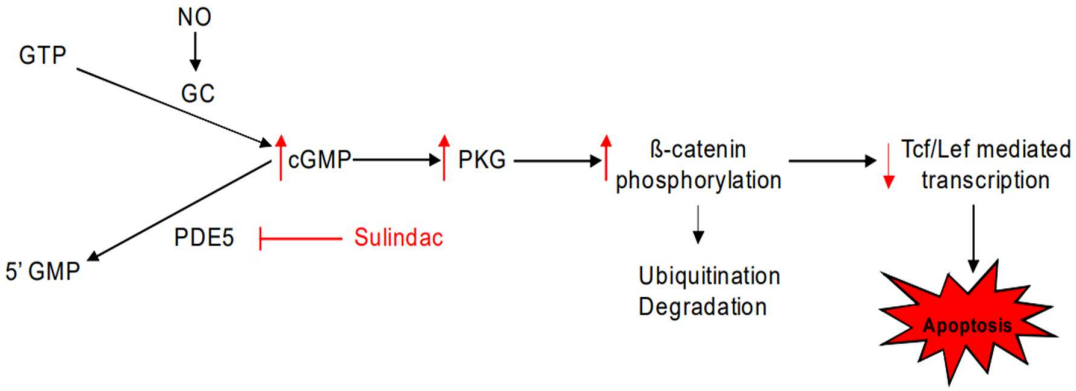


Fig 2: Proposed mechanistic framework for the apoptosis-inducing characteristics of sulindac.

"Exploring Nonsteroidal Anti-inflammatory Drugs as Cancer Combatants: Understanding Mechanisms, Pharmacology, and Clinical Considerations"

Abundant experimental, clinical, and epidemiological research suggests that NSAIDs, especially the highly targeted COX-2 inhibitors, hold potential as cancer-fighting medications. The clinical use of these medications remains restricted due to the absence of randomized trials demonstrating their effectiveness in populations beyond those with FAP and against outcomes other than colorectal polyps. Moreover, unanswered inquiries persist regarding the mechanisms of action, the most suitable drug, dosage, treatment plan, and the risk-benefit ratio in particular demographics. We anticipate that the concerns highlighted in this review will contribute to ongoing advancements in this promising field [15].

Principal Investigator: location (protocol No.)	Endpoint	Study population (Total No.)	Drug (dose),† duration	Phase	Years
Selective COX-2 inhibitors study					
Mulshine: NCI (NCI-98-C-0118)‡	Efficacy (leukoplakia reversal, histological changes,) biomarkers, safety	Oropharyngeal leukoplakia (57)	Ketorolac rinse, 3 mos	IIB	1998–2001
Boyle: Memorial Sloan-Kettering (NCI-G01-1930)	Efficacy (clinical & histological response), safety	Oral premalignant lesions (84)	Celecoxib, 12 wk	II	2000–2001
Forastiere: Johns Hopkins (NCI-P00-0145)‡	Dysplasia regression	Low or high grade Barrett's esophageal dysplasia (200)	Celecoxib, 48–96 wk	II	2000–na
Dawsey: NCI (Linxian, China) (NCI-OH95-C-N026)‡	Dysplasia regression	Esophageal squamous dysplasia (240-600)	Celecoxib and selenium, 1 y	II	1999–2000
Elmets: UAB (NCI-P00-0161)‡	Regression/prevention of actinic keratoses, biomarkers, safety	Actinic keratoses (300)	Celecoxib, 1 y	II/III	2000–na
Sabichi: M.D. Anderson (NCI-P00-0165)‡	Time to recurrence, biomarkers, toxicity	Superficial transitional cell bladder carcinoma (200)	Celecoxib, 1–2 y	II/III	2000–na
Dang: Memorial Sloan-Kettering (NCI-G00-1869)‡	Efficacy, safety	Metastatic breast cancer (12–25)	Celecoxib and trastuzumab, duration na	II	2000–na
Carducci: Johns Hopkins (NCI-P01-0186)‡	Biomarker (prostaglandin levels), toxicity	Localized prostate cancer (60–70)	Celecoxib, 6 wk	I	2001–na

*PI = principal investigator; NCI = National Cancer Institute; na = not available; UAB = University of Alabama, Birmingham.

Fig 3: Clinical experiments testing specific COX-2 inhibitors for therapeutic purposes and focusing on outcomes unrelated to colorectal adenomatous polyps or cancer.

"The Medicinal Chemistry Ramifications of Aspirin and Other NSAIDs' Anticancer Properties"

The exploration of COX inhibitors in cancer treatment and prevention presents a promising avenue for research. While COX-2 selective irreversible inhibitors offer advantages such as lipoxin generation, they may lack the non-COX dependent anti-inflammatory mechanisms found in salicylic acid. Despite potentially lower gastrointestinal side effects, they might also miss out on the anti-thrombotic effects associated with COX-1 acetylation in platelets.

However, the development of aspirin prodrugs or nitroaspirin holds potential for systemic COX inhibition with reduced GI toxicity. These compounds could offer a dual benefit of reducing colon cancer risk through lipoxin generation and mitigating cardiovascular disease through COX-1 platelet inhibition.

Furthermore, there is promise in developing NF-κB inhibitors from existing inhibitors, even without a clearly defined active site. For adenomatous polyps or colon malignancies, modified sulindac or other salicylate derivatives show considerable clinical promise. The receptor for sulindac sulfone (exisulind), though COX inactive, remains an intriguing target for future agents with tumor-suppressing properties. Lastly, the enigmatic pharmacological mechanisms of salicylic acid warrant further investigation, especially given the compelling epidemiological evidence in colorectal cancer [16].

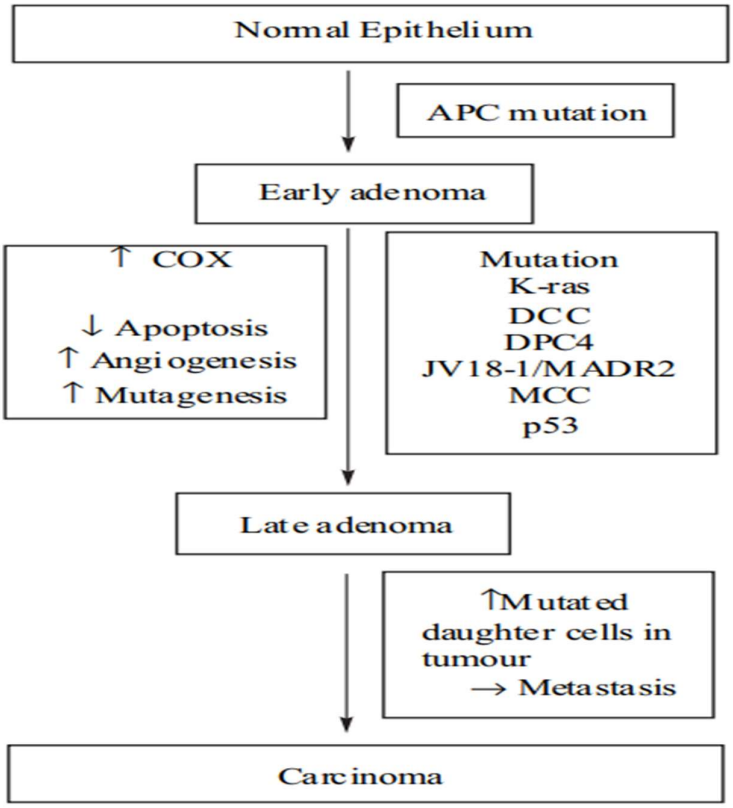


Fig 4: Fundamentals of multi-step carcinogenesis [16].

"Insights into Derivatization, Anticancer Potential, and Mechanisms of Action of Arylpropionic Acid-Derived NSAIDs"

NSAIDs have demonstrated both preventive and therapeutic effects against various cancer types, and when combined with other anticancer agents, their efficacy is further enhanced, drawing considerable interest from researchers. Among them, 2-arylpropionic acid-derived NSAIDs stand out as widely used anti-inflammatory agents, exhibiting antiproliferative effects across different cancer cell lines. Extensive research has aimed to identify the molecular targets responsible for their anticancer activity, yet the precise mechanism remains elusive. This review provides a comprehensive overview of the anticancer potential, structure-activity relationships, and synthesis of selected 2-arylpropionic acid-derived NSAID derivatives. Furthermore, it delves into non-COX targets that may mediate the anticancer effects of these derivatives. The data synthesized in this review underscore the potential of 2-arylpropionic acid-derived NSAIDs as lead compounds for the development of potent and safe anticancer agents, warranting further exploration in future research endeavors.

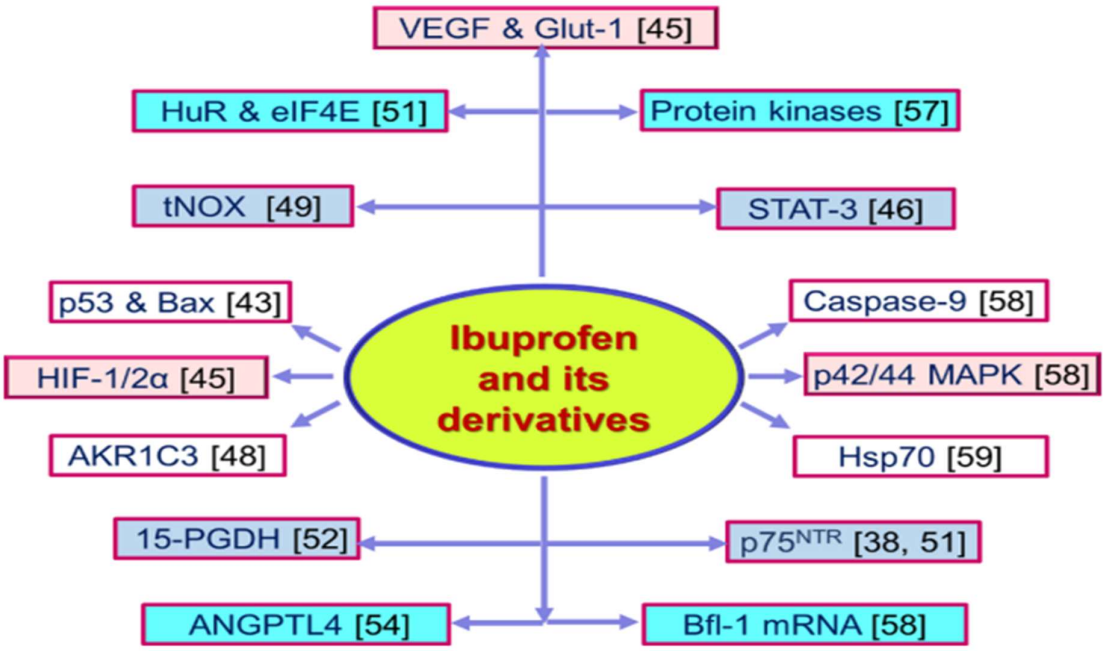


Fig 5: Various non-COX targets that may facilitate the anticancer capabilities of ibuprofen and its derivatives [17]

"The Impact of New NSAID Derivatives on Human Glioblastoma Cells in Culture: Exploring Anticancer Properties"

Several studies from epidemiology, clinical practice, and experimental research suggest that nonsteroidal anti-inflammatory drugs (NSAIDs) may possess anticancer properties. This study aimed to assess the cytotoxic potential of newly synthesized NSAID derivatives, formed by attaching α-lipoic acid (ALA) to anti-inflammatory drugs like naproxen (AL-3, 11, and 17), flurbiprofen (AL-6, 13, and 19), and ibuprofen (AL-9, 15, and 21), via a spacer molecule, in human glioblastoma cells. Additionally, the impact on gene expression levels was analyzed using quantitative real-time polymerase chain reaction (qRT-PCR). Our findings indicate that NSAID derivatives demonstrated concentration-dependent cytotoxic effects on the U87-MG cell line compared to the control group. Furthermore, treatment with the most potent compounds (AL-3, AL-6, and AL-9) led to the upregulation of the tumor suppressor gene PTEN and downregulation of certain oncogenes such as AKT1, RAF1, and EGFR. In summary, our results suggest that AL-3, AL-6, and AL-9 hold promise for further exploration as potential candidates in the development of new pharmacological strategies for cancer prevention.

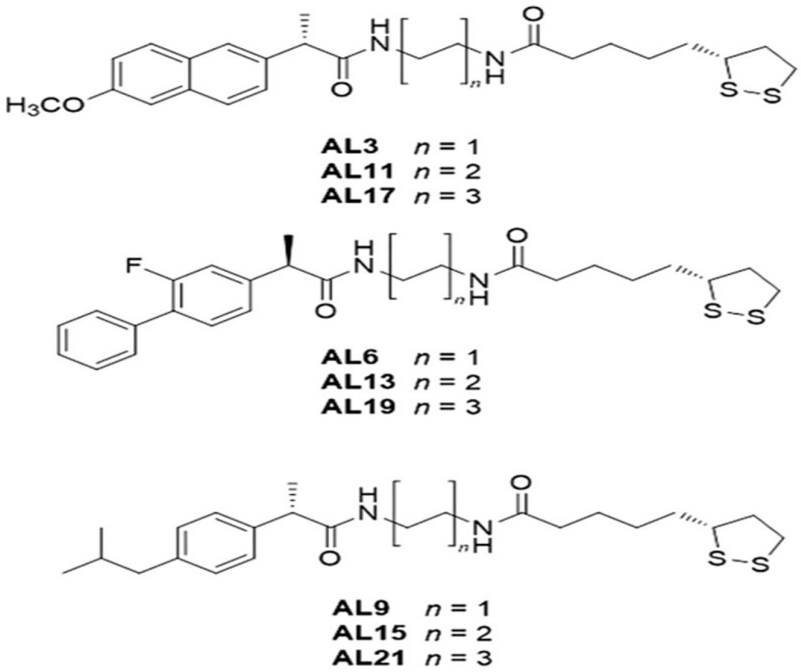


Fig 6: Structures of NSAID derivatives [18]

Future perspectives

The evolving landscape of cancer research continues to unveil promising avenues for utilizing nonsteroidal anti-inflammatory drugs (NSAIDs) as potent tools in cancer prevention and treatment. Despite the substantial strides made in understanding the anticancer properties of NSAIDs, significant challenges and opportunities lie ahead. Firstly, elucidating the precise mechanisms underlying NSAID-mediated anticancer effects remains imperative.

While cyclooxygenase (COX) inhibition has traditionally been considered the primary mechanism, emerging evidence suggests the involvement of COX-independent pathways, including phosphodiesterase-5 (PDE5) inhibition and modulation of nuclear factor kappa B (NF-κB) signaling. Further investigations into these pathways could unveil novel therapeutic targets and enhance the development of safer and more efficacious chemopreventive agents.

Moreover, personalized medicine approaches are poised to revolutionize the use of NSAIDs in cancer care. Tailoring treatment regimens based on individual risk profiles, genetic predispositions, and tumor characteristics holds the potential to optimize therapeutic outcomes while minimizing adverse effects. Integrating biomarker-driven strategies into clinical trials and practice could facilitate the identification of patient subgroups.

CONCLUSION

In conclusion, the multifaceted landscape of nonsteroidal anti-inflammatory drugs (NSAIDs) in cancer prevention and treatment presents a promising avenue for research and development. From the initial observations of sulindac's effect on colon adenomas to the exploration of COX-2 selective inhibitors, NSAIDs have demonstrated both preventive and therapeutic potential across various cancer types. However, the challenges lie in balancing their benefits with potential adverse effects, particularly gastrointestinal complications associated with traditional NSAIDs. Selective COX-2 inhibitors offer improved profiles, yet questions remain regarding their effectiveness beyond specific populations and outcomes.

Moreover, the mechanisms underlying NSAIDs' anticancer effects are complex, potentially involving COX-independent pathways such as PDE5 inhibition and downstream apoptosis induction. Future research endeavors should aim to elucidate these mechanisms further, explore derivative compounds with enhanced safety and efficacy profiles, and investigate non-COX targets to maximize NSAIDs' anticancer potential. Through continued exploration and innovation, NSAIDs may emerge as valuable assets in the ongoing fight against cancer.

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