Nonsteroidal Anti-Inflammatory Drugs in Prostate Cancer

Subjects: Oncology

Contributor: Hossein Maghsoudi , Farhad Sheikhnia , Przemysław Sitarek , Nooshin Hajmalek , Sepideh Hassani , Vahid Rashidi , Sadaf Khodagholi , Seyed Mostafa Mir , Faezeh Malekinejad , Fatemeh Kheradmand , Mansour Ghorbanpour , Navid Ghasemzadeh , Tomasz Kowalczyk

Prostate cancer (PC) is the second most common type of cancer and the leading cause of death among men worldwide. Preventing the progression of cancer after treatments such as radical prostatectomy, radiation therapy, and hormone therapy is a major concern faced by prostate cancer patients. Inflammation, which can be caused by various factors such as infections, the microbiome, obesity and a high-fat diet, is considered to be the main cause of PC. Inflammatory cells are believed to play a crucial role in tumor progression. Therefore, nonsteroidal anti-inflammatory drugs (NSAIDs) along with their effects on the treatment of inflammation-related diseases, can prevent cancer and its progression by suppressing various inflammatory pathways. Evidence shows that nonsteroidal anti-inflammatory drugs are effective in the prevention and treatment of prostate cancer.

prostate cancer nonsteroidal anti-inflammatory drugs NSAID inflammation

1. Introduction

Prostate cancer (PC) is the second most common cancer among men worldwide [1] and one of the leading causes of cancer-related death [2][3]. Significant risk factors for PC include advanced age, African American race, family history of PC, environmental factors, lifestyle, and chronic diseases [4]. Patients with late-stage PC, characterized by metastatic lesions and poorly differentiated cancer cells, typically have a poorer prognosis. However, patients in the early stages of the disease have a favorable prognosis if they undergo treatments such as radical prostatectomy, radiation therapy, and hormone therapy. These treatments can be concerning due to various complications [5][6][7]. Studies have identified inflammation as a primary cause of PC incidence. Both acute and chronic inflammation can result in the initiation and progression of PC [8][9][10][11]. Chronic inflammation increases carcinogenesis by promoting proliferation, angiogenesis, and metastasis, while also reducing the response to the immune system and chemotherapy agents [12]. Inflammation in PC is associated with various factors, including infection [13], the microbiome [14], obesity [15], and a high-fat diet (HFD) [16]. Given that inflammation is a major etiology of PC, it is believed that NSAIDs may not only reduce the incidence of cancer but also prevent cancer progression by suppressing various inflammatory pathways, including the induction of tumor cell apoptosis, DNA damage repair, and platelet activity suppression [17][18]. Numerous studies have investigated the relationship between reducing the risk of PC and the use of NSAIDs [19][20][21]. Furthermore, more than 30 epidemiological

studies, collectively describing results on over one million individuals, have identified NSAIDs as first-line chemotherapy agents against many types of cancers [22].

NSAIDs are typically categorized into several groups based on their chemical structure and selectivity: acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen), acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam), anthranilic acids (meclofenamate, mefenamic acid), naphthyl alanine (nabumetone), and selective COX-2 inhibitors (celecoxib, etoricoxib) [23] (**Figure 1**).

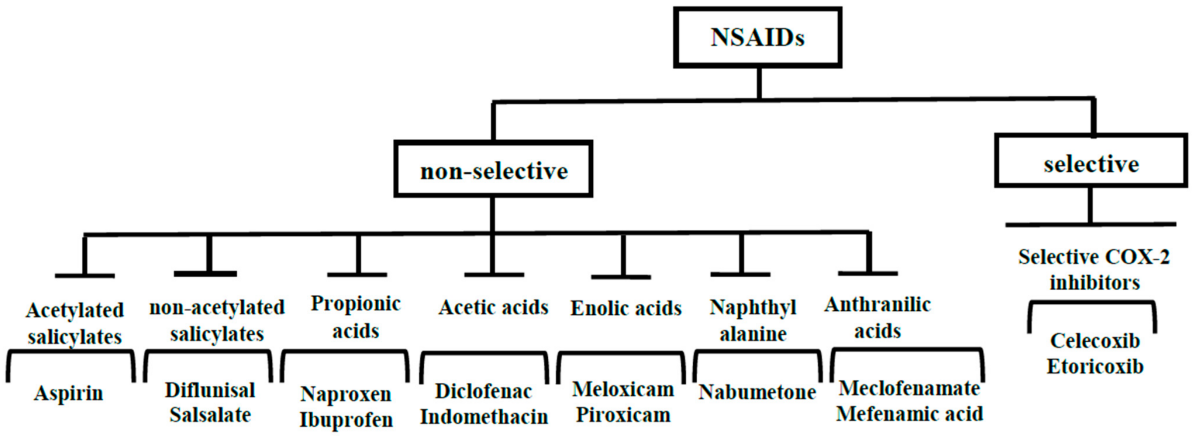

Figure 1. Classification of NSAIDs based on chemical structure and mechanism of action.

2. NSAIDs

2.1. Aspirin

In clinical practice, aspirin (ASP) is widely used to reduce the risks of cardiovascular and cerebrovascular ischemia [24]. Numerous pharmacological, clinical, and epidemiological studies have demonstrated the protective effect of ASP against several types of cancer [25]. Cyclooxygenases (COX), the targets of NSAIDs, play a key role in homeostasis, inflammation, and immune modulation [26]. Increased expression of COX-1 and COX-2 has been observed in PC [27]. Additionally, increased production of thromboxane A2 (TXA2) and prostaglandins has been associated with the progression of PC [28]. COX-1 induces platelet aggregation and facilitates the adhesion of cancer cells to endothelial cells during metastasis [29][30]. COX-2 responds to inflammatory cytokines such as IL-1α, IL-1β, TNF-α, and lipopolysaccharide and produces increased amounts of prostaglandins in inflamed tissue. COX-2 also causes an increase in the expression of Bcl-2 in PC [18][31]. The inhibition of COX-1 and COX-2 are among the primary mechanisms through which ASP is thought to prevent cell growth [32]. ASP at low doses irreversibly inhibits COX-1 activity in platelets [33]. Inhibition of the COX-1/TXA2 pathway in platelets reduces platelet aggregation in tumor cells, endothelial activation, adhesion of tumor cells to endothelium, recruitment of metastasis-promoting monocytes/macrophages, and formation of the pre-metastatic niche in prostate tissue. High doses of ASP could inhibit COX-2 [30], resulting in the prevention of the production of prostanoids (TXA2, PGF2, PGE2, PGI2, and PGD2), which play a role in reducing apoptosis and increasing cell proliferation. It has been

shown that PGE2 levels in human malignant PC tissues are 10 times higher than their levels in benign prostate tissues. PGE2 acts through receptors coupled with four G proteins named EP1, EP2, EP3, and EP4. EP3 has anti-tumor properties that can be induced by ASP. Therefore, it has been reported that ASP could exert its anti-PC properties through the activation of EP3 [34]. In another study, it was reported that ASP increased tumor necrosis factor-related ligand in PC cells by decreasing the expression of survivin, a member of the family of apoptosis-inhibiting proteins [32]. Studies have shown that ASP could inhibit the cell cycle by blocking cyclin-dependent kinases (CDKs) and causing cell cycle arrest in G0/G1 [35][36]. A retrospective case-control study demonstrated that treatment of PC cells with a combination of statin and ASP reduced both cyclin D1 expression and cell proliferation [35]. Regulatory T cells (Treg) prevent T cells from generating an effective antitumor response through immune system suppression [37][38]. A study examined the use of aspirin and statins in relation to inflammation in benign prostate tissue and revealed that aspirin could lead to a decrease in regulatory T cells [39]. COX-2/PGE2 inhibition has also been shown to reduce Treg cell activity in mouse lung cancer models [40]. In a cohort study analyzing 6594 men, ASP (low-dose < 300 mg, regular-strength 300–499 mg, extra-strength ≥ 500 mg) use was inversely associated with PC mortality [41]. Additionally, a prospective study reported that regular use of aspirin (325 mg, >3 d/wk for ≥1 yr) was associated with a reduction in the risk of lethal PC [42].

2.2. Ibuprofen

Ibuprofen (IBN), the most common NSAID, is typically administered to treat mild to moderate pain associated with a variety of conditions such as dysmenorrhea, headache, migraine, dental pain, and more [43]. IBN has also been reported to be effective in the prevention and treatment of certain cancers including colon, breast, lung, and gastric [44]. Several studies have been conducted to investigate the effects of IBN on PC. An in vitro study conducted in 2002 suggested that IBN had greater apoptotic and anti-proliferative effects on hormone-responsive cell lines (LNCaP and DU-145) compared to other NSAIDs including acetaminophen, ASP, naproxen, and NS-398 [45]. It was also reported that the anti-cancer effect of IBN treatment on PC3 and PC3 p53 +/+ cells was through cell cycle arrest at the G1/S stage, apoptosis induction via upregulation of caspase-3 and caspase-9, and inhibition of metastasis by upregulating E-cadherin [46].

2.3. Naproxen

Naproxen (NAP) has protective effects against various cancers such as bladder, breast, and colorectal [47]. Its anti-cancerous activities are due to the upregulation of p21, p53, caspase-3, IL-10 and downregulation of PCNA, CDK4, cyclin D1, and inflammatory molecules such as iNOS, TNF-α, IL-1β, IL-4, IL-6, and IL-12 [48][49][50]. Additionally, NAP suppressed PGE2, which is a key factor in tumor progression [48]. P-glycoprotein is another target of NAP [51]. NAP exerted apoptosis by initiating the cleavage of caspase-3/7, PARP-1, and inhibiting PI3K, and Bcl-2 [50].

2.4. Diclofenac

Diclofenac (DCF) is widely used as an anti-inflammatory agent in degenerative joint disease and rheumatoid arthritis [52]. Additionally, DCF is a potent analgesic drug used in physical injuries and post-surgery [53]. Various in vitro and in vivo studies confirmed the anti-cancer effects of DCF in some cancer types including neuroblastoma

[54], colon [55], ovarian [56], and pancreatic [57]. Regarding PC, one of the important studies about the anticancer effects of DCF was conducted by Arisan et al., reporting that DCF could elicit endothelial-mesenchymal transition in PC3 and PC3 p53 +/+ cells through ROS generation, upregulation of Snail, N-cadherin, and vimentin together with downregulation of E-cadherin without affecting p53. It could also arrest the cell cycle at G2/M, induce apoptosis through upregulating Fas, caspase-3, and caspase-9 as well as tumor suppressor genes (Bax, Bak, and Puma). DCF downregulated Bcl-x and Mcl-1 as well [46]. Additionally, DCF as a PPARγ antagonist in combination with rosiglitazone showed an additive inhibitory effect on thymidine incorporation into DNA in PC3 cells, whereas DCF antagonized the inhibitory effect of rosiglitazone on DU-145 cells [58][59].

2.5. Indomethacin

Indomethacin (IND) currently has therapeutic efficacy against severe osteoarthritis, rheumatoid arthritis, gouty arthritis, or ankylosing spondylitis [60].

AKR1C3 is an enzyme that is involved in the biosynthesis of potent androgens such as testosterone and dihydrotestosterone (DHT) and also catalyzes the conversion of PGH2 to PGF2α, which is crucial for PC cells to proliferate [61][62]. AKR1C3 has been reported to be elevated in CRPC patients and is considered as a therapeutic target in these patients [63]. It is proposed that inhibition of this bifunctional enzyme may be useful in both androgen-sensitive and androgen-insensitive conditions [64].

DU-145 overexpressing AKR1C3 cells have been shown to resist radiation therapy by enhancing the MAPK signaling pathway and inhibiting the PPARγ pathway. IND suppressed the resistance of these cells to irradiation by inhibiting AKR1C3 [61]. IND in DuCaP cells promoted apoptosis by increasing activated caspases-3 and -7 [63]. IND significantly decreased PSA mRNA and protein levels in VCaP cells [65].

2.6. Mefenamic Acid

Mefenamic acid (MFA) is an NSAID that relieves dental and menstrual pain and is typically administered orally [66]. This drug has a significant protective effect against increasing lipid peroxidation, protein oxidation, TNF-α and IL-1β levels, and ultimately reduces inflammation [67][68]. In addition, it can reduce cancer cell proliferation, progression, angiogenesis, and invasion [69]. It has also been shown that MFA in combination with ionizing radiation increases apoptosis in tumor tissues and protects against DNA damage caused by ionizing radiation [70][71]. MFA is a class of NSAIDs that has high antiproliferative activity, whereas salicylates, the most common drugs used in clinical studies, show a relatively weak antiproliferative effect [72]. MFA has been reported to act as a signaler for apoptosis by inhibiting calcium uptake in cells. On the other hand, it causes apoptosis by cleaving procaspase-3 and PARP-1 [73]. MFA was found to be effective in the treatment of PC in in vitro and in vivo models [74]. As mentioned earlier, inflammation is an essential component of PC, and it has been reported that MFA reduces its biochemical progression [75].

2.7. Celecoxib

Celecoxib (CXB), a member of NSAIDs that specifically inhibits cyclooxygenase-2 (COX-2), has been proposed for the treatment of several neoplasms, including prostate, colorectal, breast, lung, stomach, head and neck cancers, as well as for the prevention of prostate, colorectal, breast, lung and skin cancers [76][77][78][79][80][81][82][83]. Studies have shown that CXB is effective in treating familial adenomatous polyposis, osteoarthritis, rheumatoid arthritis, primary dysmenorrhea and acute pain [84][85][86][87]. In comparison to other NSAIDs such as diclofenac, ibuprofen and naproxen, CXB has demonstrated greater absorption into the prostate in an animal study and is more suitable for chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) [88]. Additionally, CXB has shown greater cytotoxicity when compared to other cyclooxygenase inhibitors [89].

The possible anti-prostate cancer mechanisms of NSAIDs that have been discussed in various investigations are summarized in **Table 1** and **Figure 2**.

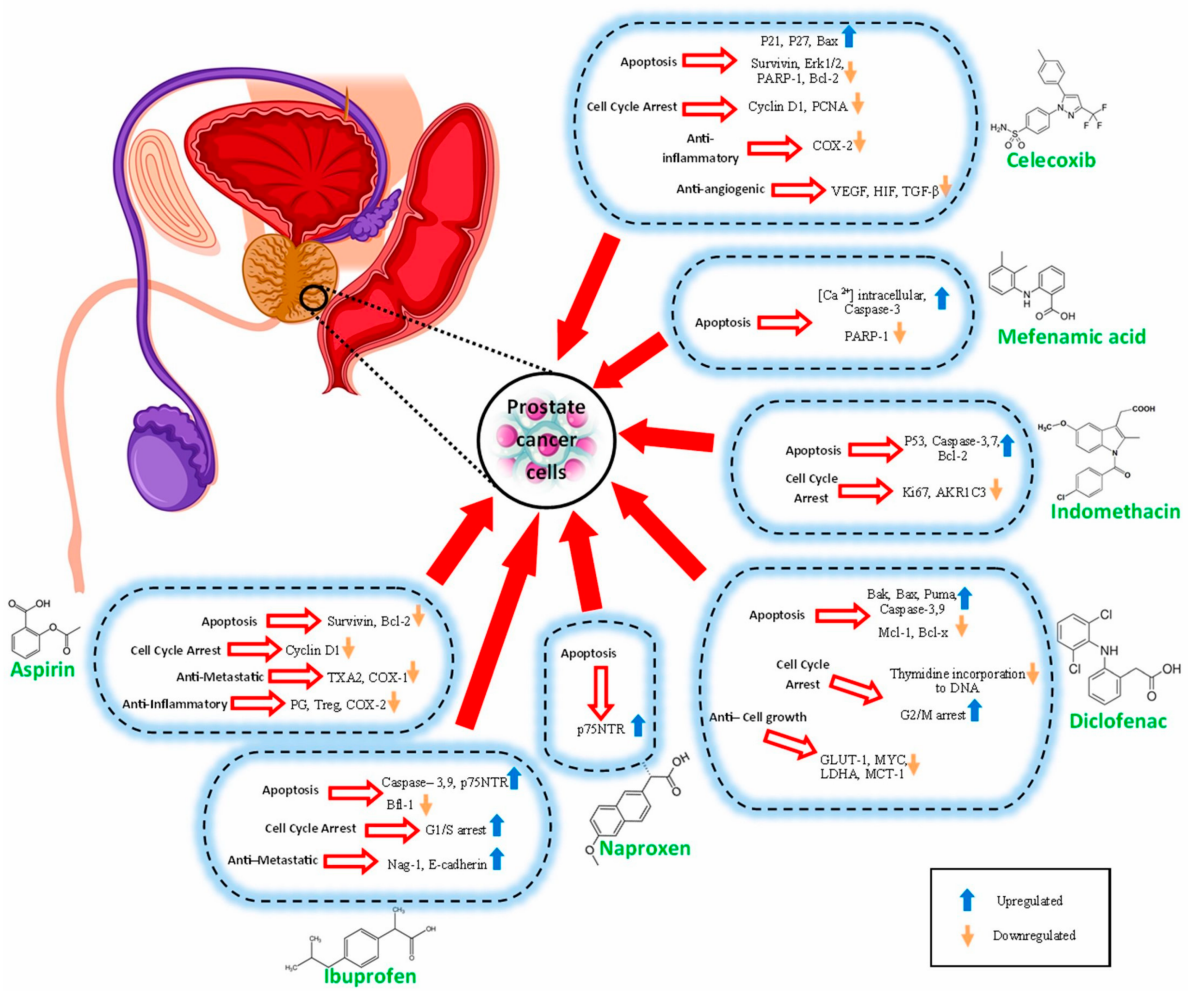

Figure 2. Schematic representation of the mechanisms of action of different NSAIDs in prostate cancer.

Table 1. Anti-prostate cancer mechanisms of NSAIDs; upregulation, downregulation.

Effects / NSAIDs	Apoptosis	Cell Cycle Arrest	Anti-Metastatic	Anti-Cell Growth	Anti-Inflammatory	Anti-Angiogenic
ASP	Survivin, Bcl-2	Cyclin D1	TXA2, COX-1		PG, Treg, COX-2	
IBN	Caspase-3,9, p75NTR Bfl-1	G1/S arrest	Nag-1, E-cadherin			
NAP	p75NTR					
DCF	Bak, Bax, Puma, Caspase-3,9 Mcl-1, Bcl-x	Thymidine incorporation to DNA G2/M arrest		GLUT-1, MYC, LDHA, MCT-1		
IND	P53, Caspase-3,7, Bcl-2	Ki67, AKR1C3				
MFA	$[Ca^{2+}]$ intracellular, Caspase-3 PARP-1					
CXB	P21, P27, Bax. Survivin, Erk1/2, PARP-1, Bcl-2	Cyclin D1, PCNA			COX-2	VEGF, HIF-1, TGF-β

References

3. Adverse Effects of NSAIDs

Chronic usage of NSAIDs adversely affects several organs mainly the gastrointestinal (GI), cardiovascular (CV), cerebrovascular, and renal systems; however, short-term medications and therapeutic doses could be well-tolerated [90]. The range of GI side effects differs from mild, including nausea and dyspepsia, to severe conditions like GI bleeding, perforated peptic ulcer, and iron deficiency anemia secondary to the bleeding [91]. These complications result from reduced COX-1 mucosal protective prostaglandins and decreased bicarbonate production in the stomach and small intestine. CXB is associated with minimal GI complications [92]. Among non-selective NSAIDs, DCF and NAP are the most vulnerable, whereas IBN has been reported to be safer [93].

The NSAIDs-linked renal adverse effects are acute renal failure, fluid and electrolyte (e.g., sodium and potassium) retention, GFR reduction, interstitial nephritis, papillary necrosis, and chronic renal disease [90]. Acute renal failure as the most reported NSAIDs renal complication was related to NAP and IBN [94][95], whereas, the high dose of CXB (400 mg twice a day for six months) in a man with stage two prostate carcinoma did not have a significant effect on GFR [78]. Additionally, hypertension, atrial fibrillation, myocardial infarction, thrombotic problems caused by an imbalance between PGI2 and TXA2 production in favor of thrombosis, and heart failure have been documented [96]. Furthermore, various investigations demonstrated that cerebrovascular complications such as hemorrhagic stroke were associated with some NSAIDs in which the smallest risk was attributed to CXB and the highest to IBN, DCF, NAP, and ketoprofen [97].

To prevent the aforementioned complications, using NSAIDs at the lowest therapeutic dose for a short period is recommended [98]. Additionally, the co-administration of certain agents like proton pump inhibitors (e.g., omeprazole, and pantoprazole), protective agents (e.g., misoprostol), as well as H2 receptor blockers (e.g., famotidine) will reduce the GI, especially upper GI adverse effects [99].

In the studies previously mentioned pertaining to prostate cancer, NSAIDs were generally well-tolerated. However, additional clinical trials are necessary to further ascertain the safety profile of these drugs.

1. Siegel, R.; Miller, K.; Jemal, A. Cancer statistics. 2020 CA Cancer J. Clin. Am. Cancer Soc. 2020, 70, 7–30.
2. Virtanen, V.; Paunu, K.; Ahlskog, J.K.; Varnai, P.; Sipeky, C.; Sundvall, M. PARP inhibitors in prostate cancer–the preclinical rationale and current clinical development. Genes 2019, 10, 565.
3. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F.; Bsc, M.F.B.; Me, J.F.; Soerjomataram, M.I., et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA A Cancer J. Clin. 2021, 71, 209–249.
4. Giri, V.N.; Beebe-Dimmer, J.L. (Eds.) Familial Prostate Cancer. Seminars in Oncology; Elsevier: Amsterdam, The Netherlands, 2016.
5. De Carlo, F.; Celestino, F.; Verri, C.; Masedu, F.; Liberati, E.; Di Stasi, S.M. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: Surgical, oncological, and functional outcomes: A systematic review. Urol. Int. 2014, 93, 373–383.
6. Amin, N.P.; Sher, D.J.; Konski, A.A. Systematic review of the cost effectiveness of radiation therapy for prostate cancer from 2003 to 2013. Appl. Health Econ. Health Policy 2014, 12, 391–408.
7. Mitsuzuka, K.; Arai, Y. Metabolic changes in patients with prostate cancer during androgen deprivation therapy. Int. J. Urol. 2018, 25, 45–53.
8. De Marzo, A.M.; Platz, E.A.; Sutcliffe, S.; Xu, J.; Grönberg, H.; Drake, C.G.; Nakai, Y.; Isaacs, W.B.; Nelson, W.G. Inflammation in prostate carcinogenesis. Nat. Rev. Cancer 2007, 7, 256–269.
9. Nakai, Y.; Nonomura, N. Inflammation and prostate carcinogenesis. Int. J. Urol. 2013, 20, 150–160.
10. Taverna, G.; Pedretti, E.; Di Caro, G.; Borroni, E.M.; Marchesi, F.; Grizzi, F. Inflammation and prostate cancer: Friends or foe? Inflamm. Res. 2015, 64, 275–286.
11. Schillaci, O.; Scimeca, M.; Trivigno, D.; Chiaravalloti, A.; Facchetti, S.; Anemona, L.; Bonfiglio, R.; Santeusanio, G.; Tancredi, V.; Bonanno, E.; et al. Prostate cancer and inflammation: A new molecular imaging challenge in the era of personalized medicine. Nucl. Med. Biol. 2019, 68, 66–79.
12. Balkwill, F.; Mantovani, A. Inflammation and cancer: Back to Virchow? Lancet 2001, 357, 539–545.
13. Koul, H.; Kumar, B.; Koul, S.; Deb, A.; Hwa, J.; Maroni, P.; van Bokhoven, A.; Lucia, M.; Kim, F.; Meacham, R. The role of inflammation and infection in prostate cancer: Importance in prevention, diagnosis and treatment. Drugs Today 2010, 46, 929–943.

14. Sfanos, K.S.; Yegnasubramanian, S.; Nelson, W.G.; De Marzo, A.M. The inflammatory microenvironment and microbiome in prostate cancer development. Nat. Rev. Urol. 2018, 15, 11–24.
15. Fujita, K.; Hayashi, T.; Matsushita, M.; Uemura, M.; Nonomura, N. Obesity, inflammation, and prostate cancer. J. Clin. Med. 2019, 8, 201.
16. Narita, S.; Nara, T.; Sato, H.; Koizumi, A.; Huang, M.; Inoue, T.; Habuchi, T. Research evidence on high-fat diet-induced prostate cancer development and progression. J. Clin. Med. 2019, 8, 597.
17. Kashfi, K. Anti-inflammatory agents as cancer therapeutics. Adv. Pharmacol. 2009, 57, 31–89.
18. Zhang, Z.; Chen, F.; Shang, L. Advances in antitumor effects of NSAIDs. Cancer Manag. Res. 2018, 10, 4631.
19. Choe, K.S.; Cowan, J.E.; Chan, J.M.; Carroll, P.R.; D'Amico, A.V.; Liauw, S.L. Aspirin use and the risk of prostate cancer mortality in men treated with prostatectomy or radiotherapy. J. Clin. Oncol. 2012, 30, 3540.
20. Cardwell, C.R.; Flahavan, E.M.; Hughes, C.M.; Coleman, H.G.; O'sullivan, J.M.; Powe, D.G.; Murray, L.J. Low-dose aspirin and survival in men with prostate cancer: A study using the UK Clinical Practice Research Datalink. Cancer Causes Control. 2014, 25, 33–43.
21. Flahavan, E.; Bennett, K.; Sharp, L.; Barron, T. A cohort study investigating aspirin use and survival in men with prostate cancer. Ann. Oncol. 2014, 25, 154–159.
22. Ashok, V.; Dash, C.; Rohan, T.E.; Sprafka, J.M.; Terry, P.D. Selective cyclooxygenase-2 (COX-2) inhibitors and breast cancer risk. Breast 2011, 20, 66–70.
23. Ghlichloo, I.; Gerriets, V. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs); StatPearls Publishing: Treasure Island, FL, USA, 2019.
24. Di Bella, S.; Luzzati, R.; Principe, L.; Zerbato, V.; Meroni, E.; Giuffrè, M.; Crocè, L.S.; Merlo, M.; Perotto, M.; Dolso, E.; et al. Aspirin and Infection: A Narrative Review. Biomedicines 2022, 10, 263.
25. Menter, D.G.; Bresalier, R.S. An Aspirin a Day: New Pharmacological Developments and Cancer Chemoprevention. Annu. Rev. Pharmacol. Toxicol. 2022, 63, 165–186.
26. Malkowski, M.G. The Cyclooxygenases. In Encyclopedia of Inorganic and Bioinorganic Chemistry; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2011; pp. 1–18.
27. Kirschenbaum, A.; Klausner, A.P.; Lee, R.; Unger, P.; Yao, S.; Liu, X.H.; Levine, A.C. Expression of cyclooxygenase-1 and cyclooxygenase-2 in the human prostate. Urology 2000, 56, 671–676.
28. Greenhough, A.; Smartt, H.J.; Moore, A.E.; Roberts, H.R.; Williams, A.C.; Paraskeva, C.; Kaidi, A. The COX-2/PGE 2 pathway: Key roles in the hallmarks of cancer and adaptation to the tumour

microenvironment. Carcinogenesis 2009, 30, 377–386.

29. Morita, I. Distinct functions of COX-1 and COX-2. Prostaglandins Other Lipid Mediat. 2002, 68, 165–175.
30. Lucotti, S.; Cerutti, C.; Soyer, M.; Gil-Bernabé, A.M.; Gomes, A.L.; Allen, P.D.; Smart, S.; Markelc, B.; Watson, K.; Armstrong, P.C.; et al. Aspirin blocks formation of metastatic intravascular niches by inhibiting platelet-derived COX-1/thromboxane A 2. J. Clin. Investig. 2019, 129, 1845–1862.
31. Fujita, H.; Koshida, K.; Keller, E.T.; Takahashi, Y.; Yoshimito, T.; Namiki, M.; Mizokami, A. Cyclooxygenase-2 promotes prostate cancer progression. Prostate 2002, 53, 232–240.
32. Bilani, N.; Bahmad, H.; Abou-Kheir, W. Prostate cancer and aspirin use: Synopsis of the proposed molecular mechanisms. Front. Pharmacol. 2017, 8, 145.
33. Rauzi, F.; Kirkby, N.S.; Edin, M.L.; Whiteford, J.; Zeldin, D.C.; Mitchell, J.A.; Warner, T.D. Aspirin inhibits the production of proangiogenic 15 (S)-HETE by platelet cyclooxygenase-1. FASEB J. 2016, 30, 4256–4266.
34. Kashiwagi, E.; Shiota, M.; Yokomizo, A.; Itsumi, M.; Inokuchi, J.; Uchiumi, T.; Naito, S. Prostaglandin receptor EP3 mediates growth inhibitory effect of aspirin through androgen receptor and contributes to castration resistance in prostate cancer cells. Endocr. Relat. Cancer 2013, 20, 431–441.
35. Olivan, M.; Rigau, M.; Colás, E.; Garcia, M.; Montes, M.; Sequeiros, T.; Regis, L.; Celma, A.; Planas, J.; Placer, J.; et al. Simultaneous treatment with statins and aspirin reduces the risk of prostate cancer detection and tumorigenic properties in prostate cancer cell lines. BioMed Res. Int. 2015, 2015, 762178.
36. Shiff, S.J.; Koutsos, M.I.; Qiao, L.; Rigas, B. Nonsteroidal antiinflammatory drugs inhibit the proliferation of colon adenocarcinoma cells: Effects on cell cycle and apoptosis. Exp. Cell Res. 1996, 222, 179–188.
37. Kalinski, P. Regulation of immune responses by prostaglandin E2. J. Immunol. 2012, 188, 21–28.
38. Sutmuller, R.; Garritsen, A.; Adema, G.J. Regulatory T cells and toll-like receptors: Regulating the regulators. Ann. Rheum. Dis. 2007, 66 (Suppl. S3), iii91–iii95.
39. Hurwitz, L.M.; Kulac, I.; Gumuskaya, B.; Valle, J.A.B.D.; Benedetti, I.; Pan, F.; Liu, J.O.; Marrone, M.T.; Arnold, K.B.; Goodman, P.J.; et al. Use of Aspirin and Statins in Relation to Inflammation in Benign Prostate Tissue in the Placebo Arm of the Prostate Cancer Prevention TrialAspirin and Statin Use and Intraprostatic Inflammation. Cancer Prev. Res. 2020, 13, 853–862.
40. Sharma, S.; Yang, S.C.; Zhu, L.; Reckamp, K.; Gardner, B.; Baratelli, F.; Huang, M.; Batra, R.K.; Dubinett, S.M. Tumor cyclooxygenase-2/prostaglandin E2–dependent promotion of FOXP3

expression and CD4+ CD25+ T regulatory cell activities in lung cancer. Cancer Res. 2005, 65, 5211–5220.

41. Hurwitz, L.M.; Joshu, C.E.; Barber, J.R.; Prizment, A.E.; Vitolins, M.Z.; Jones, M.R.; Folsom, A.R.; Han, M.; Platz, E.A. Aspirin and Non-Aspirin NSAID Use and Prostate Cancer Incidence, Mortality, and Case Fatality in the Atherosclerosis Risk in Communities StudyAspirin and Prostate Cancer Incidence and Mortality. Cancer Epidemiol. Biomark. Prev. 2019, 8, 563–569.
42. Downer, M.K.; Allard, C.B.; Preston, M.A.; Gaziano, J.M.; Stampfer, M.J.; Mucci, L.A.; Batista, J.L. Regular aspirin use and the risk of lethal prostate cancer in the physicians' health study. Eur. Urol. 2017, 72, 821–827.
43. Bushra, R.; Aslam, N. An overview of clinical pharmacology of ibuprofen. Oman Med. J. 2010, 25, 155.
44. Raegg, C.; Dormond, O. Suppression of tumor angiogenesis by nonsteroidal anti-inflammatory drugs: A new function for old drugs. Sci. World J. 2001, 1, 808–811.
45. Andrews, J.; Djakiew, D.; Krygier, S.; Andrews, P. Superior effectiveness of ibuprofen compared with other NSAIDs for reducing the survival of human prostate cancer cells. Cancer Chemother. Pharmacol. 2002, 50, 277–284.
46. Arisan, E.D.; Akar, R.O.; Rencuzogullari, O.; Yerlikaya, P.O.; Gurkan, A.C.; Akın, B.; Dener, E.; Kayhan, E.; Unsal, N.P. The molecular targets of diclofenac differs from ibuprofen to induce apoptosis and epithelial mesenchymal transition due to alternation on oxidative stress management p53 independently in PC3 prostate cancer cells. Prostate Int. 2019, 7, 156–165.
47. Espinosa-Cano, E.; Huerta-Madronal, M.; Camara-Sanchez, P.; Seras-Franzoso, J.; Schwartz, S., Jr.; Abasolo, I.; San Román, J.; Aguilar, M.R. Hyaluronic acid (HA)-coated naproxen-nanoparticles selectively target breast cancer stem cells through COX-independent pathways. Mater. Sci. Eng. C 2021, 124, 112024.
48. Mohammed, A.; Janakiram, N.B.; Madka, V.; Zhang, Y.; Singh, A.; Biddick, L.; Li, Q.; Lightfoot, S.; Steele, V.E.; Lubet, R.A.; et al. Intermittent Dosing Regimens of Aspirin and Naproxen Inhibit Azoxymethane-Induced Colon Adenoma Progression to Adenocarcinoma and Invasive CarcinomaAspirin and Naproxen Dosing Regimens for Prevention of CRC. Cancer Prev. Res. 2019, 12, 751–762.
49. Suh, N.; Reddy, B.S.; DeCastro, A.; Paul, S.; Lee, H.J.; Smolarek, A.K.; So, J.Y.; Simi, B.; Wang, C.X.; Janakiram, N.B.; et al. Combination of Atorvastatin with Sulindac or Naproxen Profoundly Inhibits Colonic Adenocarcinomas by Suppressing the p65/β-Catenin/Cyclin D1 Signaling Pathway in RatsAtorvastatin, with Sulindac or Naproxen, Inhibits Colon Cancer. Cancer Prev. Res. 2011, 4, 1895–1902.

50. Kim, M.S.; Kim, J.E.; Lim, D.Y.; Huang, Z.; Chen, H.; Langfald, A.; Lubet, R.A.; Grubbs, C.J.; Dong, Z.; Bode, A.M. Naproxen Induces Cell-Cycle Arrest and Apoptosis in Human Urinary Bladder Cancer Cell Lines and Chemically Induced Cancers by Targeting PI3KNaproxen Targets PI3K to Prevent Urinary Bladder Cancer. Cancer Prev. Res. 2014, 7, 236–245.
51. Zrieki, A.; Farinotti, R.; Buyse, M. Cyclooxygenase inhibitors down regulate P-glycoprotein in human colorectal Caco-2 cell line. Pharm. Res. 2008, 25, 1991–2001.
52. Pantziarka, P.; Sukhatme, V.; Bouche, G.; Meheus, L.; Sukhatme, V.P. Repurposing Drugs in Oncology (ReDO)—Diclofenac as an anti-cancer agent. Ecancermedicalscience 2016, 10, 610.
53. Barden, J.; Edwards, J.; Moore, R.; McQuay, H. Single dose oral diclofenac for postoperative pain. Cochrane Database Syst. Rev. 2004, CD004768.
54. Johnsen, J.I.; Lindskog, M.; Ponthan, F.; Pettersen, I.; Elfman, L.; Orrego, A.; Sveinbjörnsson, B.; Kogner, P. NSAIDs in neuroblastoma therapy. Cancer Lett. 2005, 228, 195–201.
55. Lanas, A. Nonsteroidal antiinflammatory drugs and cyclooxygenase inhibition in the gastrointestinal tract: A trip from peptic ulcer to colon cancer. Am. J. Med. Sci. 2009, 338, 96–106.
56. Valle, B.L.; D'Souza, T.; Becker, K.G.; Wood, W.H., III; Zhang, Y.; Wersto, R.P.; Morin, P.J. Non-steroidal anti-inflammatory drugs decrease E2F1 expression and inhibit cell growth in ovarian cancer cells. PLoS ONE 2013, 8, e61836.
57. Mayorek, N.; Naftali-Shani, N.; Grunewald, M. Diclofenac inhibits tumor growth in a murine model of pancreatic cancer by modulation of VEGF levels and arginase activity. PLoS ONE 2010, 5, e12715.
58. Lea, M.A.; Sura, M.; Desbordes, C. Inhibition of cell proliferation by potential peroxisome proliferator-activated receptor (PPAR) gamma agonists and antagonists. Anticancer. Res. 2004, 24, 2765–2772.
59. Adamson, D.J.; Frew, D.; Tatoud, R.; Wolf, C.R.; Palmer, C.N. Diclofenac antagonizes peroxisome proliferator-activated receptor-γ signaling. Mol. Pharmacol. 2002, 61, 7–12.
60. Gebril, S.M.; Ito, Y.; Shibata, M.; Maemura, K.; Abu-Dief, E.E.; Hussein, M.R.A.; Abdelaal, U.M.; Elsayed, H.M.; Otsuki, Y.; Higuchi, K. Indomethacin can induce cell death in rat gastric parietal cells through alteration of some apoptosis-and autophagy-associated molecules. Int. J. Exp. Pathol. 2020, 101, 230–247.
61. Sun, S.-Q.; Gu, X.; Gao, X.-S.; Li, Y.; Yu, H.; Xiong, W.; Yu, H.; Wang, W.; Li, Y.; Teng, Y.; et al. Overexpression of AKR1C3 significantly enhances human prostate cancer cells resistance to radiation. Oncotarget 2020, 7, 48050, Erratum in Oncotarget 2020, 11, 1575.
62. Liu, C.; Lou, W.; Zhu, Y.; Yang, J.C.; Nadiminty, N.; Gaikwad, N.W.; Evans, C.P.; Gao, A.C. Intracrine androgens and AKR1C3 activation confer resistance to enzalutamide in prostate

cancer. Cancer Res. 2015, 75, 1413–1422.

63. Hamid, A.R.A.H.; Pfeiffer, M.J.; Verhaegh, G.W.; Schaafsma, E.; Brandt, A.; Sweep, F.C.G.J.; Sedelaar, J.P.M.; Schalken, J.A. Aldo-keto reductase family 1 member C3 (AKR1C3) is a biomarker and therapeutic target for castration-resistant prostate cancer. Mol. Med. 2012, 18, 1449–1455.
64. Liedtke, A.J.; Adeniji, A.O.; Chen, M.; Byrns, M.C.; Jin, Y.; Christianson, D.W.; Marnett, L.J.; Penning, T.M. Development of potent and selective indomethacin analogues for the inhibition of AKR1C3 (type 5 17β-hydroxysteroid dehydrogenase/prostaglandin F synthase) in castrate-resistant prostate cancer. J. Med. Chem. 2013, 56, 2429–2446.
65. Cai, C.; Chen, S.; Ng, P.; Bubley, G.J.; Nelson, P.S.; Mostaghel, E.A.; Marck, B.; Matsumoto, A.M.; Simon, N.I.; Wang, H.; et al. Intratumoral De Novo Steroid Synthesis Activates Androgen Receptor in Castration-Resistant Prostate Cancer and Is Upregulated by Treatment with CYP17A1 InhibitorsProstate Cancer Resistance to CYP17A1 Inhibitors. Cancer Res. 2011, 71, 6503–6513.
66. Cimolai, N. The potential and promise of mefenamic acid. Expert Rev. Clin. Pharmacol. 2013, 6, 289–305.
67. Armagan, G.; Turunc, E.; Kanit, L.; Yalcin, A. Neuroprotection by mefenamic acid against D-serine: Involvement of oxidative stress, inflammation and apoptosis. Free. Radic. Res. 2012, 46, 726–739.
68. Asanuma, M.; Nishibayashi-Asanuma, S.; Miyazaki, I.; Kohno, M.; Ogawa, N. Neuroprotective effects of non-steroidal anti-inflammatory drugs by direct scavenging of nitric oxide radicals. J. Neurochem. 2001, 76, 1895–1904.
69. Patel, S.S.; Tripathi, R.; Chavda, V.K.; Savjani, J.K. Anticancer Potential of Mefenamic Acid Derivatives with Platelet-Derived Growth Factor Inhibitory Property. Anticancer Agents Med. Chem. 2020, 20, 998–1008.
70. Hosseinimehr, S.J.; Nobakht, R.; Ghasemi, A.; Pourfallah, T.A. Radioprotective effect of mefenamic acid against radiation-induced genotoxicity in human lymphocytes. Radiat. Oncol. J. 2015, 33, 256.
71. Seyyedi, R.; Amiri, F.T.; Farzipour, S.; Mihandoust, E.; Hosseinimehr, S.J. Mefenamic acid as a promising therapeutic medicine against colon cancer in tumor-bearing mice. Med. Oncol. 2022, 39, 18.
72. Čeponytė, U.; Paškevičiūtė, M.; Petrikaitė, V. Comparison of NSAIDs activity in COX-2 expressing and non-expressing 2D and 3D pancreatic cancer cell cultures. Cancer Manag. Res. 2018, 10, 1543.

73. Woo, D.H.; Han, I.-S.; Jung, G. Mefenamic acid-induced apoptosis in human liver cancer cell-lines through caspase-3 pathway. Life Sci. 2004, 75, 2439–2449.
74. Soriano-Hernández, A.D.; Galvan-Salazar, H.R.; Montes-Galindo, D.A.; Rodriguez-Hernandez, A.; Martinez-Martinez, R.; Guzman-Esquivel, J.; Valdez-Velazquez, L.L.; Baltazar-Rodriguez, L.M.; Espinoza-Gómez, F.; Rojas-Martinez, A.; et al. Antitumor effect of meclofenamic acid on human androgen-independent prostate cancer: A preclinical evaluation. Int. Urol. Nephrol. 2012, 44, 471–477.
75. Melnikov, V.; Tiburcio-Jimenez, D.; A Mendoza-Hernandez, M.; Delgado-Enciso, J.; De-Leon-Zaragoza, L.; Guzman-Esquivel, J.; Rodriguez-Sanchez, I.P.; Martinez-Fierro, M.L.; Lara-Esqueda, A.; Delgado-Enciso, O.G.; et al. Improve cognitive impairment using mefenamic acid non-steroidal anti-inflammatory therapy: Additional beneficial effect found in a controlled clinical trial for prostate cancer therapy. Am. J. Transl. Res. 2021, 13, 4535.
76. Quiñones, O.G.; Pierre, M.B. Cutaneous application of celecoxib for inflammatory and cancer diseases. Curr. Cancer Drug Targets 2019, 19, 5–16.
77. Tołoczko-Iwaniuk, N.; Dziemiańczyk-Pakieła, D.; Nowaszewska, B.K.; Celińska-Janowicz, K.; Miltyk, W. Celecoxib in cancer therapy and prevention–review. Curr. Drug Targets 2019, 20, 302–315.
78. Benson, P.; Yudd, M.; Sims, D.; Chang, V.; Srinivas, S.; Kasimis, B. Renal effects of high-dose celecoxib in elderly men with stage D2 prostate carcinoma. Clin. Nephrol. 2012, 78, 376–381.
79. Atari-Hajipirloo, S.; Nikanfar, S.; Heydari, A.; Kheradmand, F. Imatinib and its combination with 2,5-dimethyl-celecoxibinduces apoptosis of human HT-29 colorectal cancer cells. Res. Pharm. Sci. 2017, 12, 67–73.
80. Atari-Hajipirloo, S.; Nikanfar, S.; Heydari, A.; Noori, F.; Kheradmand, F. The effect of celecoxib and its combination with imatinib on human HT-29 colorectal cancer cells: Involvement of COX-2, Caspase-3, VEGF and NF-κB genes expression. Cell. Mol. Biol. 2016, 62, 68–74.
81. Mohammadian, M.; Zeynali, S.; Azarbaijani, A.F.; Ansari, M.H.K.; Kheradmand, F. Cytotoxic effects of the newly-developed chemotherapeutic agents 17-AAG in combination with oxaliplatin and capecitabine in colorectal cancer cell lines. Res. Pharm. Sci. 2017, 12, 517.
82. Nikanfar, S.; Atari-Hajipirloo, S.; Kheradmand, F.; Rashedi, J.; Heydari, A. Cytotoxic effect of 2, 5-dimethyl-celecoxib as a structural analog of celecoxib on human colorectal cancer (HT-29) cell line. Cell. Mol. Biol. 2018, 64, 8–13.
83. Nikanfar, S.; ATARI-HAJIPIRLOO, S.; KHERADMAND, F.; HEYDARI, A. Imatinib Synergizes with 2, 5-Dimethylcelecoxib, a Close Derivative of Celecoxib, in HT-29 Colorectal Cancer Cells: Involvement of Vascular Endothelial Growth Factor. J. Res. Pharm. 2023, 27, 948–956.

84. Zielinski, S.L. Despite positive studies, popularity of chemoprevention drugs increasing slowly. J. Natl. Cancer Inst. 2004, 96, 1410–1412.

85. Steinbach, G.; Lynch, P.M.; Phillips, R.K.; Wallace, M.H.; Hawk, E.; Gordon, G.B.; Wakabayashi, N.; Saunders, B.; Shen, Y.; Fujimura, T.; et al. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N. Engl. J. Med. 2000, 342, 1946–1952.

86. Henney, J.E. Celecoxib indicated for FAP. JAMA 2000, 283, 1131.

87. Smith, M.R.; Manola, J.; Kaufman, D.S.; Oh, W.K.; Bubley, G.J.; Kantoff, P.W. Celecoxib versus placebo for men with prostate cancer and a rising serum prostate-specific antigen after radical prostatectomy and/or radiation therapy. J. Clin. Oncol. 2006, 24, 2723–2728.

88. Yellepeddi, V.K.; Radhakrishnan, J.; Radhakrishnan, R. Penetration and pharmacokinetics of non-steroidal anti-inflammatory drugs in rat prostate tissue. Prostate 2018, 78, 80–85.

89. Brizzolara, A.; Benelli, R.; Venè, R.; Barboro, P.; Poggi, A.; Tosetti, F.; Ferrari, N. The ErbB family and androgen receptor signaling are targets of Celecoxib in prostate cancer. Cancer Lett. 2017, 400, 9–17.

90. Harirforoosh, S.; Asghar, W.; Jamali, F. Adverse effects of nonsteroidal antiinflammatory drugs: An update of gastrointestinal, cardiovascular and renal complications. J. Pharm. Pharm. Sci. 2013, 16, 821–847.

91. Fernandes, D.C.; Norman, A.J. Drug-induced gastrointestinal disorders. Medicine 2019, 47, 301–308.

92. Tai, F.W.D.; McAlindon, M.E. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. Clin. Med. 2021, 21, 131.

93. Masso Gonzalez, E.L.; Patrignani, P.; Tacconelli, S.; Rodríguez, L.A.G. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. Arthritis Rheum. 2010, 62, 1592–1601.

94. Antonucci, R.; Cuzzolin, L.; Arceri, A.; Dessì, A.; Fanos, V. Changes in urinary PGE 2 after ibuprofen treatment in preterm infants with patent ductus arteriosus. Eur. J. Clin. Pharmacol. 2009, 65, 223–230.

95. Horbach, S.J.; Lopes, R.D.; Guaragna, J.C.D.C.; Martini, F.; Mehta, R.H.; Petracco, J.B.; Bodanese, L.C.; Adauto Filho, C.; Cirenza, C.; de Paola, A.A.; et al. Naproxen as prophylaxis against atrial fibrillation after cardiac surgery: The NAFARM randomized trial. Am. J. Med. 2011, 124, 1036–1042.

96. Varga, Z.; rafay ali Sabzwari, S.; Vargova, V.; Sabzwari, S.R.A. Cardiovascular risk of nonsteroidal anti-inflammatory drugs: An under-recognized public health issue. Cureus 2017, 9, e1144.

97. Fanelli, A.; Ghisi, D.; Aprile, P.L.; Lapi, F. Cardiovascular and cerebrovascular risk with nonsteroidal anti-inflammatory drugs and cyclooxygenase 2 inhibitors: Latest evidence and clinical implications. Ther. Adv. Drug Saf. 2017, 8, 173–182.
98. Vonkeman, H.E.; van de Laar, M.A. (Eds.) Nonsteroidal Anti-Inflammatory Drugs: Adverse Effects and Their Prevention; Seminars in arthritis and rheumatism; Elsevier: Amsterdam, The Netherlands, 2010.
99. Lanas, A.; Hunt, R. Prevention of anti-inflammatory drug-induced gastrointestinal damage: Benefits and risks of therapeutic strategies. Ann. Med. 2006, 38, 415–428.