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REVIEW

Aspirin in Cancer Therapy: Pharmacology and Nanotechnology Advances

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Abstract: Aspirin, a non-steroidal anti-inflammatory drug (NSAID), has garnered significant attention for its anti-cancer potential. This review explores the pharmacological properties, chemical dynamics, and evolving therapeutic applications of aspirin, with an emphasis on its integration into advanced cancer therapies. Aspirin demonstrates broad-spectrum efficacy across diverse cancer types by modulating signaling pathways such as COX-dependent and COX-independent mechanisms, including Wnt, NF-κB, β-catenin/TCF, and IL-6/STAT3. Recent advancements highlight the role of nanotechnology in enhancing aspirin's targeted delivery, therapeutic effectiveness, and patient outcomes. Nanoparticle-based formulations, including liposomes, solid lipid nanoparticles, and mesoporous silica nanoparticles, offer improved solubility, stability, and bioavailability, enabling controlled drug release and tumor-specific targeting. These innovations reduce systemic toxicity and enhance therapeutic effects, paving the way for aspirin's integration into personalized cancer treatments. Ongoing clinical studies reinforce its safety profile, underscoring aspirin's role in cancer pharmacotherapy. This review calls for continued research into aspirin's repurposing in combination therapies and novel delivery systems to maximize its therapeutic potential.

Keywords: aspirin, cancer therapy, signaling pathways, nanotechnology, targeted drug delivery

Introduction

Aspirin (acetylsalicylic acid, C₉H₈O₄)¹ is one of the most widely used medications worldwide, known for its analgesic,² anti-inflammatory,³ and antipyretic effects.^{4,5} It is a key component of the World Health Organization's List of Essential Medicines due to its safety, efficacy, and affordability. While traditionally used for pain relief, fever reduction, and cardiovascular protection, recent research has highlighted aspirin's promising role in cancer prevention and treatment. Long-term studies have shown that regular aspirin use can reduce the risk of cancers, particularly colorectal cancer, and is now being investigated for its potential to inhibit tumor growth, metastasis, and inflammation in various cancer types. The anticancer effects of aspirin are largely attributed to its inhibition of cyclooxygenase enzymes (COX-1 and COX-2),^{1,6} particularly COX-2, which is often overexpressed in tumors. COX-2 mediates the production of pro-inflammatory prostaglandins, which promote tumor growth, angiogenesis, and metastasis. By inhibiting COX-2, aspirin not only reduces inflammation but also disrupts tumor-promoting signaling pathways, including those involved in DNA repair, apoptosis, and cell cycle regulation. Additionally, aspirin reflects antiplatelet effect by preventing thrombus formation in cardiovascular conditions.⁷ It demonstrates this effect by inhibition of thromboxane A2 synthesis in the platelets.⁸ In recent years, a growing interest regarding the practical utility of aspirin as primary and secondary prevention of cancer has boosted its research in anti-cancer strategies.⁹ The anti-cancer potential of aspirin is a consequence of aspirin-mediated inhibition of various signaling pathways, including β-catenin/TCF pathway¹⁰ and the IL-6/STAT3 pathway.¹¹ Clinical evidence supports aspirin's role in lowering cancer incidence, especially in the colorectal, breast, and gastric cancers. Furthermore, aspirin has shown potential in enhancing the efficacy of chemotherapeutic agents, suggesting its utility as an adjunct therapy in cancer treatment.¹

In recent years, however, there has been growing interest in the development of innovative formulations and delivery systems to enhance aspirin's anticancer efficacy and minimize its adverse effects. One of the most promising strategies is the integration of nanotechnology, which offers a means to overcome many of the limitations associated with conventional aspirin

therapy. Nanotechnology allows for the design of aspirin-loaded nanocarriers, such as liposomes,¹² solid lipid nanoparticles (SLNs)¹³, mesoporous silica nanoparticles (MSNs)^{14,15} and dendrimers, which significantly improve the drug's solubility, stability, and bioavailability. These nanocarriers can be tailored for targeted drug delivery, allowing aspirin to be directed specifically to cancer cells or tumor sites, thus minimizing systemic toxicity and enhancing therapeutic outcomes.

Nanotechnology not only improves aspirin's delivery but also facilitates controlled and sustained drug release, which is crucial for maintaining therapeutic concentrations at the tumor site over extended periods.¹⁶ This targeted approach improves the accumulation of aspirin in the tumor microenvironment, increasing its anticancer effects while reducing side effects associated with systemic drug administration. In addition to monotherapy, aspirin-loaded nanoparticles can be used in combination with other anticancer agents, such as chemotherapeutic drugs, to create synergistic treatment strategies.¹⁷

Aspirin-based nanomedicines are also being explored in various cancer types, including colorectal,¹⁸ breast, lung, and pancreatic cancers.¹⁷ For example, aspirin encapsulated in thermoresponsive liposomes has been shown to enhance tumor cell apoptosis under mild hyperthermia,¹⁹ while aspirin-loaded mesoporous silica nanoparticles have been used to improve drug delivery in liver cancer therapy.¹⁵ Additionally, aspirin-loaded nanoparticles combined with other bioactive molecules, such as curcumin²⁰ or resveratrol,²¹ have demonstrated enhanced anticancer effects in preclinical models. This growing body of evidence highlights the potential of aspirin in cancer nanotherapy, emphasizing its ability to serve as a key component in personalized, targeted treatment regimens with reduced systemic toxicity and improved efficacy.

Chemical Properties and Salt Forms of Aspirin

Aspirin (acetylsalicylic acid, C₉H₈O₄) is a widely used anti-inflammatory drug that has a molecular weight of approximately 180.16 g/mol.^{22,23} It appears as a crystalline powder that is odorless in its pure form but may develop an acetic acid-like smell in the presence of moisture, which can occur due to the hydrolysis of aspirin.^{24,25} While aspirin is only sparingly soluble in water (3 g in 1 liter),²⁶ it demonstrates marked solubility in organic solvents such as ethanol and acetone, making it more accessible for various pharmaceutical formulations. As a weak acid, aspirin has an acid dissociation constant (pKa) of 3.5 at 25 °C,²⁷ meaning it can undergo dissociation in acidic environments, which is central to its therapeutic effects. In dry conditions, aspirin remains stable, but it hydrolyzes when exposed to moisture, which limits its shelf-life and storage conditions. It also undergoes decomposition in the presence of alkaline solutions, emphasizing its reactivity due to the presence of the ester functional group. Aspirin's reactivity contributes to its broad therapeutic applications, allowing it to undergo hydrolysis, esterification, and other reactions depending on the chemical environment. These properties not only give aspirin its anti-inflammatory, analgesic, and antipyretic effects but also provide the basis for its use in both acute and chronic conditions. One of the significant advances in aspirin formulations involves the use of various salt forms that improve its solubility, stability, and bioavailability. These salts, such as sodium acetylsalicylate,²⁸ calcium acetylsalicylate,²⁹ magnesium acetylsalicylate,³⁰ lysine acetylsalicylate,³¹ and choline magnesium trisalicylate,³² enhance aspirin's absorption and therapeutic action compared to its unaltered form. The structural differences between aspirin and its salts influence their pharmacokinetics, offering faster absorption and less gastrointestinal irritation, which is a common side effect of regular aspirin formulations. The salt forms of aspirin are presented in Figure 1 highlight aspirin's versatility, enabling modifications for improved bioavailability, stability, and therapeutic effectiveness.

Aspirin and Its Derivatives/Analogs in Cancer Therapy

Aspirin has long been recognized for its anticancer properties, primarily through its ability to inhibit cyclooxygenase (COX) enzymes, especially COX-2, which are involved in inflammation and tumorigenesis. However, the development of aspirin derivatives has garnered increasing attention due to their ability to enhance anticancer efficacy, reduce toxicity, and offer targeted action. Nitric oxide-donating aspirin derivatives (NO-ASA) have been developed to improve aspirin's anticancer potential, especially in genetically predisposed cancers. In studies involving mismatch repair (MMR)-deficient hereditary nonpolyposis colorectal cancer (HNPCC) cells, NO-ASA demonstrated strong dose-dependent suppression of microsatellite instability (MSI), reducing instability by up to 67% after 19–20 weeks, outperforming aspirin's comparatively weak effects.³³ Additionally, the para-isomer (p-NO-ASA) exhibited potent anticancer activity, particularly against

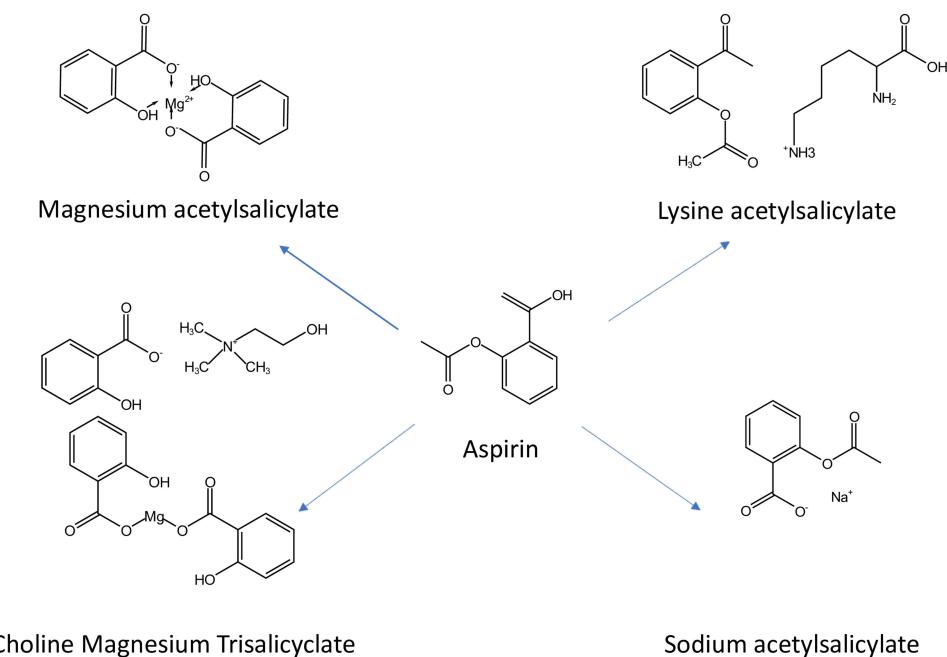


Figure 1 Aspirin and its salt forms structures. This illustrates the chemical salt forms of aspirin, including Magnesium Acetylsalicylate, Lysine Acetylsalicylate, Choline Magnesium Trisalicylate, and Sodium Acetylsalicylate. These forms are derived from the central compound aspirin, shown in the center, with arrows representing the conversion pathways to their respective derivatives. Each chemical structure displays the molecular composition of the salts, highlighting their functional groups and ionized states.

estrogen receptor-negative (ER-) breast cancer cells (MDA-MB-231 and SK-BR-3), where it achieved IC₅₀ values of 13 and 17 μM, compared to >3000 μM for aspirin. In vivo, p-NO-ASA inhibited NF-κB activation, induced apoptosis, and generated reactive oxygen species (ROS), showcasing its significant anticancer effects.³⁴

Another promising derivative, NCX-4016, a nitric oxide-releasing aspirin derivative, demonstrated superior efficacy in a rat model of colon cancer. NCX-4016 reduced aberrant crypt foci by 85%, compared to aspirin's 64% reduction.³⁵ This result was attributed to its ability to release nitric oxide, enhancing tumor suppression without causing the gastrointestinal irritation typically associated with aspirin. The novel Phosphoaspirin derivative showed remarkable anticancer efficacy, exhibiting 18- to 144-fold more potent growth inhibition across multiple cancer cell lines (colon, lung, liver, pancreas, breast) compared to conventional aspirin.³⁶ This suggests that phosphoaspirin may overcome some of the limitations of traditional aspirin in cancer therapy by offering more targeted action. Similarly, piperidone-salicylate conjugates, synthesized from acetylsalicylate derivatives, exhibited potent antiproliferative effects against A431, HCT116, and MCF7 cancer cell lines by arresting the cell cycle at the G1 or S-phase. These conjugates also served as multi-targeted tyrosine kinase inhibitors, specifically targeting VEGFR-2 and EGFR, further broadening the therapeutic potential of aspirin-based compounds.³⁷

A novel diaspirin (BCS) derivative was explored for its effects on colorectal cancer (SW480) cells, demonstrating greater toxicity than aspirin. This compound induced both necrotic and apoptotic pathways, indicating its potential to induce cell death more effectively than the parent compound.³⁸ In a similar vein, NCX-4040, another nitric oxide-releasing derivative, exhibited high cytotoxicity across colon, bladder, and pancreatic cancer cell lines, utilizing a mitochondria-dependent pro-apoptotic pathway for its anticancer activity.³⁹ A particularly interesting advancement is NOSH-aspirin, a hybrid molecule releasing both nitric oxide (NO) and hydrogen sulfide (H₂S). This derivative has shown a remarkable 9000-fold increase in efficacy compared to aspirin alone. NOSH-aspirin effectively inhibited cell proliferation, induced apoptosis, and caused G₀/G₁ cell cycle arrest in colon cancer cells. In vivo studies revealed that NOSH-aspirin reduced tumor volume by 85% in mice with human colon cancer xenografts, demonstrating its promise for overcoming the limitations of traditional aspirin therapy.^{12,40} It also exhibited superior chemopreventive effects compared to aspirin, with significantly reduced gastrointestinal toxicity.⁴¹ Two aspirin analogues, PN517 and PN524,

demonstrated increased toxicity against oesophageal cancer cell lines. These analogues selectively targeted cancer cells and showed synergistic effects with cisplatin and oxaliplatin in both oesophageal and colorectal cancer (CRC) cell lines, enhancing the potential for combinatorial cancer therapies.⁴² Another interesting compound, the aspirin-chalcone conjugate, displayed strong anticancer activity against breast cancer (MDA-MB-468). This conjugate induced G1/S cell cycle arrest and triggered apoptosis through modulation of caspase-3, p53, and Bax/Bcl-2 pathways, highlighting its therapeutic value in breast cancer treatment.⁴³ The 6d derivative, explored for its microtubule-destabilizing potential, exhibited strong anticancer effects by inhibiting tubulin polymerization ($IC_{50} = 1.065 \text{ ng/mL}$), disrupting the microtubule network and ultimately arresting cancer cell division.⁴³ Similarly, the resveratrol-based aspirin prodrug (RAH) demonstrated superior anticancer activity compared to aspirin or resveratrol alone, effectively reducing cell proliferation through cyclin downregulation and inducing apoptosis via caspase-3 activation.²¹ Finally, Hydrogen sulfide-releasing aspirin (HS-ASA) was shown to have significant anticancer activity, especially against estrogen receptor-negative (ER-) breast cancer. It promoted G0/G1 cell cycle arrest, apoptosis, and reduced NF- κ B expression in MDA-MB-231 cells, offering a potential therapeutic option for this aggressive cancer subtype.⁴⁴ Aspirin derivatives have been extensively modified to improve efficacy and reduce adverse effects. These modifications, such as NO-releasing variants, curcumin conjugates, and phosphoaspirin, are depicted in Figure 2. The structures illustrate functional groups designed for specific therapeutic enhancements, highlighting aspirin's versatility as a drug platform. An Overview of the efficacy of aspirin derivatives and analogs for different cancer are shown in Table 1.

Aspirin in Nanotechnology in Cancer Therapy

Nanotechnology has significantly advanced the application of aspirin in cancer therapy by improving its delivery, stability, bioavailability, and efficacy while minimizing systemic side effects. These advancements not only address the limitations of traditional aspirin use but also open new avenues for targeted, controlled, and combinational therapeutic strategies. An aspirin-loaded, double-modified nano-delivery system using galactosamine-modified polydopamine-coated mesoporous silica nanoparticles (Gal-PDA-MSN) was developed for hepatocellular carcinoma. This pH-sensitive system demonstrated enhanced drug release in acidic environments, with superior toxicity to HepG2 liver cancer cells compared to free aspirin. The platform highlights a promising controlled release and targeted therapeutic approach in liver cancer.¹⁵ Similarly, thermo-responsive liposomes (Asp/TLs), with a size of ~114 nm and 84% encapsulation efficiency, selectively released aspirin under mild hyperthermia (40°C), leading to a fourfold increase in cytotoxicity against triple-negative breast cancer (MDA-MB-231). These liposomes modulated gene expression, significantly upregulating pro-apoptotic genes (Bak, Bax, P53) and downregulating anti-apoptotic genes (BCL-xL, BCL-2), making them a promising option for hyperthermia-assisted cancer treatment.¹⁹

The dextran-aspirin nanomedicine (P3C-Asp) demonstrated its potential in colorectal cancer (CRC) therapy by releasing salicylic acid, scavenging reactive oxygen species (ROS), and restoring gut microbiota balance. It increased beneficial bacteria like *Lactobacillus* and *Akkermansia*, achieving a 2.1-fold higher tumor suppression rate than free aspirin and synergizing with αPD-L1 therapy to extend survival. This approach underscores the dual benefits of gut inflammation modulation and immune regulation in CRC.^{18,45} Aspirin-loaded cross-linked lipoic acid nanovesicles (Asp@cLANVs) combined cancer cell eradication with microenvironment modulation, addressing postsurgical cancer recurrence. This dual-functional nanodrug reduced recurrence rates to 33.3% compared to 100% with cisplatin, significantly extending survival in preclinical models.⁴⁶ Chondroitin sulfate–glycyrrhetic acid dual ligand-modified liposomes (CS–GA–LIP), co-delivering aspirin and curcumin, targeted both cancer cells and platelets in hepatocellular carcinoma. These nanoparticles (~133 nm) inhibited platelet activation, tumor proliferation, migration, and angiogenesis while downregulating MMP-2 expression, demonstrating potent therapeutic effects against pulmonary metastasis.²⁰ In colorectal cancer therapy, Eudragit L100-coated chitosan nanoparticles loaded with quercetin and aspirin provided pH-dependent drug release, reducing inflammatory markers like PGE2, IL-8, and TNF, and reversing histological damage. This formulation highlights the synergistic potential of quercetin and aspirin in nanotechnology-driven platforms for colonic cancer treatment.⁴⁷

Theranostic platforms further amplify aspirin's role in cancer therapy. A structure-switching aptamer biosensor enabled real-time detection of proinflammatory cytokine IFN-γ, coupled with controlled aspirin release, demonstrating

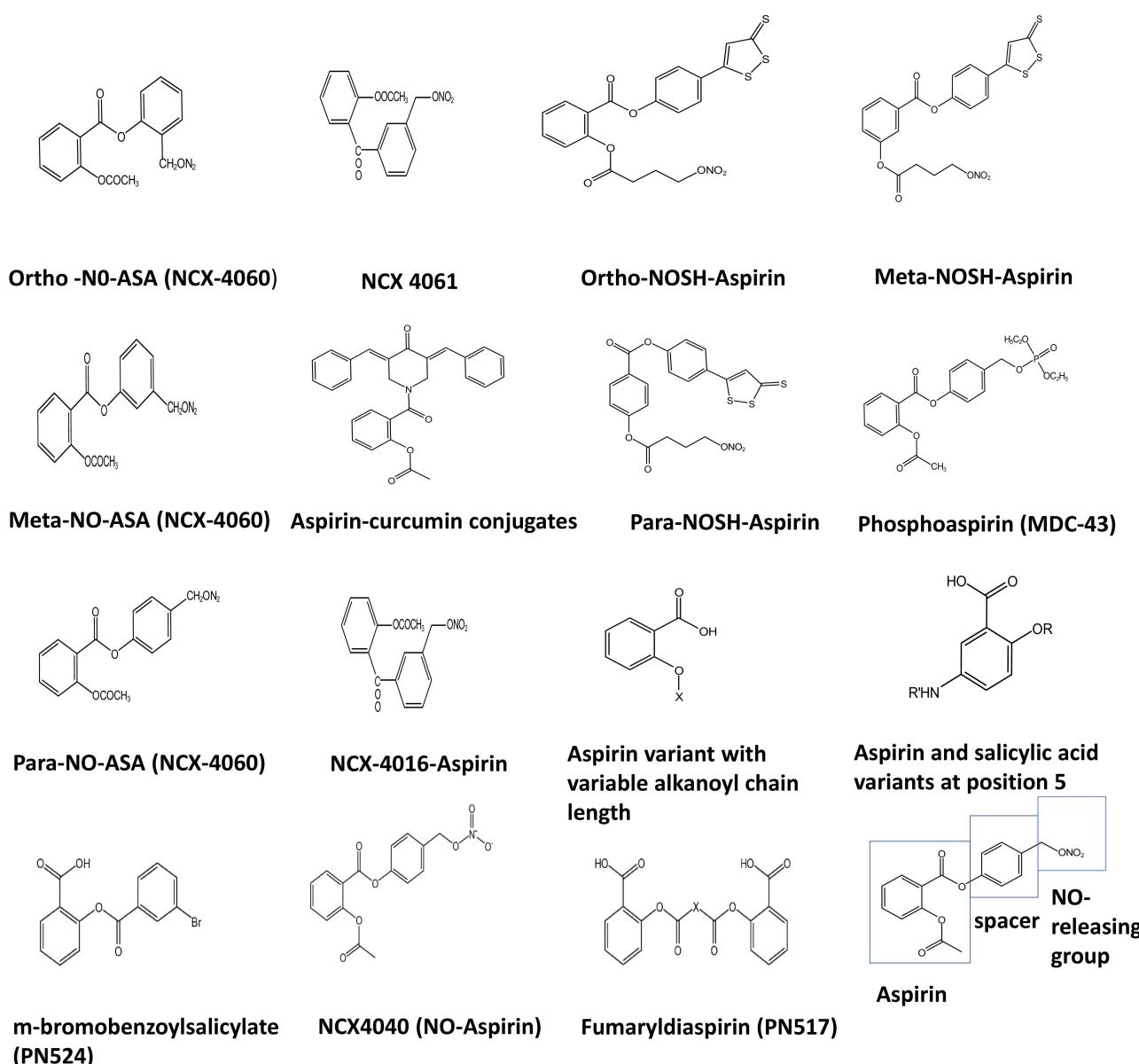


Figure 2 Chemical Structures of Analogs and Derivative Forms of Aspirin. This figure illustrates the chemical structures of aspirin derivatives, including NO-releasing variants (eg. Ortho-NO-ASA, Meta-NO-ASA, Para-NO-ASA), curcumin conjugates, phosphoaspirin, and other functionalized aspirin molecules such as NCX-4040 and fumarylidiaspirin. These derivatives are designed to enhance aspirin's pharmacological properties, such as anti-inflammatory, analgesic, and antiplatelet effects, while minimizing side effects. Structural modifications include NO-releasing groups, alkanoyl chain extensions, and conjugation with bioactive compounds like curcumin.

high sensitivity (10 pg/mL) and effective inflammation inhibition in a rat model. This approach offers potential for personalized, cytokine-guided anti-inflammatory therapy.⁴⁸ Another biomimetic nanoplatform (TAFL), combining tumor-derived exosome fusion liposomes with aspirin and photothermal agents (TPE-BBT), addressed cancer stem cell (CSC)-mediated recurrence and metastasis post-FLASH-RT. Laser-triggered aspirin release synergized with photothermal therapy to induce apoptosis, DNA damage, and reduced CSC stemness, significantly decreasing tumor recurrence and metastasis.⁴⁹

Advanced co-delivery systems like thiolated disulfide-bridged nanoparticles loaded with aspirin and metformin demonstrated improved pharmacokinetics, achieving over 96% drug release, enhanced AUC, and superior inhibition of epithelial-mesenchymal transition (EMT) markers such as E-cadherin and Vimentin, offering a promising solution for colorectal cancer.⁵⁰ Similarly, nanoamorphous exosomal platforms improved aspirin's solubility, cellular uptake, and cancer stem cell eradication, achieving significant apoptosis and autophagy induction in breast and colorectal cancer

Table I Overview of the Efficacy of Aspirin Derivatives in Different Cancer

Aspirin Derivative	Mechanism/Effects	Model	Cell Line/Mouse Model Used	Concentration	Efficacy Compared to Aspirin
NO-ASA	Suppresses microsatellite instability (MSI) in mismatch repair (MMR)-deficient cells	In vitro	Murine Embryonic Fibroblasts (MEFs), E1A-transformed MEFs, colonocyte cell lines from p53 ^{-/-} and p53 ^{-/-} Msh2 ^{-/-} mice, HCT116 (hMLH1 ^{-/-}), HCT116 (hMLH1 ^{-/-})+chr2 (hMLH1 ^{-/-}), and HCT116 (hMLH1 ^{-/-})+chr3 (hMLH1 ⁺)	–	300- to 3000-fold more effective
NCX-4016	Reduces aberrant crypt foci without COX inhibition, provides analgesic effects	Rat colon cancer model	–	10 mg/kg)	85% reduction vs aspirin's 64%
Phosphoaspirin (P-ASA)	Increases ROS, induces apoptosis, cell cycle arrest, targets mitochondria	In vitro	HT-29, LoVo, HCT116, HCT-15, SW480 (colorectal), BxPC-3, MIA PaCa-2 (pancreatic), MCF-7 (breast), Hep G2 (liver), and H838 (lung).	P-ASA in each cell line are as follows: HT-29: 42.6 ± 10.6 μM, HCT-15: 14.3 ± 6.7 μM, SW480: 23.1 ± 3.9 μM, LoVo: 46.6 ± 7.3 μM, HCT116: 67.6 ± 10.4 μM, BxPC3: 27.4 ± 6.3 μM, MIA PaCa-2: 113 ± 17.8 μM, HepG2: 13.8 ± 5.8 μM, H838: 54.0 ± 4.5 μM, and MCF-7: 38.0 ± 5.1 μM	18- to 144-fold more potent
Piperidone-Salicylate Conjugates BCS (Diaspirin)	Multi-target tyrosine kinase inhibitors; arrest cell cycle at G1/S Induces necrotic and apoptotic pathways	In vitro In vitro	A431, HCT116, MCF7 SW480 (colon cancer), U373 (astrocytoma, grade III), MCF7 (breast cancer), and MDA-MB-231 (breast cancer)	– 1mM	Up to 12.9-fold more potent than Sunitinib Greater toxicity than aspirin
NOSH-Aspirin	Releases NO and H ₂ S, inducing apoptosis and cell cycle arrest	In vitro	HT-29	7.7–45.5 nM	9000-fold greater efficacy
NCX 4040	Mitochondria-dependent pro-apoptotic pathway, synergizes with oxaliplatin	In vitro	LoVo, WiDr, and LRVWZ (a doxorubicin-resistant line derived from LoVo).	5–50μM	Strong cytotoxicity, enhanced oxaliplatin efficacy
Aspirin-Chalcone Conjugate (6d)	Induces apoptosis, inhibits tubulin polymerization	Breast cancer	MDA-MB-468	IC50 = 1.065 ng/mL	Potent microtubule-destabilizing agent
Resveratrol-Based Aspirin Prodrug (RAH)	Downregulates cyclins, induces caspase-3 mediated apoptosis	In vitro, In vivo	HCT-116	–	Safer, enhanced anticancer properties
HS-ASA	Induces G0/G1 arrest, promotes apoptosis, reduces NF-κB	In vivo, In vitro	MDA-MB-231 (human breast cancer) and HMEpC (normal human mammary epithelial).	0.1–100000μM	Significant tumor reduction
NOSH-Aspirin (NBS-1120)	Superior chemopreventive effects, minimal gastrotoxicity	In vivo	Male Wistar rats	477 mg/kg	85% tumor volume reduction
Aspirin with Nanotechnology	Co-encapsulation with curcumin enhances stability and delivery	In vitro	ES-2 and SKOV3	56.1 μg/mL and 52.5 μg/mL	Synergistic mitochondrial apoptosis
Aspirin-Paclitaxel Nanoparticle	Synergistic sensitization, enhances apoptosis	In vitro	LL/2	25.62μg mL ⁻¹	17.7-fold reduction in PTX's IC50
Aspirin-Curcumin-Sulforaphane in c-SLNs	Safe for long-term chemoprevention	In vivo	BALB/c mice	ACS c-SLNs were orally administered to male and female BALB/c mice at the doses of low (2+4.5+0.16 mg/kg), medium (20+45+1.6 mg/kg), and high (60+135+4.8 mg/kg) for 3 days, 28 days, and 90 days	No toxicity in chronic tests

cells.⁵¹ Combinatorial strategies have further enhanced aspirin's therapeutic potential. Nano-encapsulated combinations of ferulic acid and aspirin reduced pancreatic cancer cell viability by 70% with 8- to 40-fold lower doses compared to free agents, highlighting their synergistic action through NF-κB downregulation.⁵² Aspirin encapsulated in solid lipid nanoparticles (SLNs) combined with curcumin and sulforaphane significantly enhanced chemopreventive effects in pancreatic cancer, increasing apoptosis by 61% in MIA PaCa-2 and Panc-1 cells.¹³ Chitosan-coated SLNs co-encapsulating aspirin, curcumin, and sulforaphane (ACS c-SLNs) reduced tumor incidence by 83.4% in a pancreatic ductal adenocarcinoma mouse model without inducing toxicity, demonstrating their safety and efficacy for long-term prevention.^{17,53}

Targeted therapies leveraging folic acid-functionalized aspirin-loaded mesoporous silica nanoparticles (MNP-Asp-PD-PG-F) enhanced tumor-specific uptake via receptor-mediated endocytosis in breast cancer cells, improving cytotoxicity and reducing proliferation.¹⁴ Additionally, folic acid-positive targeting by FA-BSA@DA nanoplatforms enabled H₂O₂-triggered aspirin release, effectively inhibiting heparanase to prevent lung metastasis in breast cancer.⁵⁴ Nanotechnology also addresses inflammation-related pathways in cancer. Aspirin-loaded bovine serum albumin nanoparticles (BSA-NPs) reduced NF-κB p65, MMP-2, and MMP-9 expression levels, significantly inhibiting cancer cell invasion in transwell and scratch-wound assays.⁵⁵ Another innovative platform using polypyrrole-coated mesoporous TiO₂ nanocomposites loaded with aspirin and doxorubicin achieved enhanced tumor inhibition through photothermal conversion and sonodynamic effects.⁵⁶ Aspirin co-encapsulated with curcumin in mPEG-PLGA nanoparticles (SH-ASA) induced mitochondrial apoptosis in ovarian cancer cells, offering a promising clinical application for this nanotechnology-driven approach.⁵⁷

Mechanistically, nanotechnology-driven aspirin formulations improve DNA repair and reduce damage. Nano-aspirin significantly decreased DNA damage and micronucleus formation while increasing p53 expression, inhibiting inflammation-related pathways.⁵⁸ Studies on nanoamorphous exosomal delivery systems confirmed the enhanced efficacy of poorly soluble aspirin, showcasing its potential in clinical translation.⁵⁹ Lastly, aspirin and curcumin encapsulated in PLGA nanoparticles, combined with sulforaphane, showed synergistic effects in colorectal cancer cell lines SW-480 and HT-29, reducing viability by up to 61%.⁶⁰ Aptamer-functionalized nanoparticles loaded with ursolic acid and aspirin prodrugs demonstrated enhanced synergistic effects, both in vitro and in vivo, for targeted cancer therapy.^{61,62} An overview of aspirin based nanotechnological formulation for cancer therapy are shown in Table 2.

Molecular Mechanism of Aspirin

Aspirin, also known as acetylsalicylic acid⁶³ exhibits its effects by employing primary mode of action involving the inhibition of cyclooxygenases (COX-1 and COX-2).⁶ Beyond its well-characterized COX-dependent mechanisms, aspirin also engages in COX-independent pathways.⁶⁴ The diversified mechanisms of Aspirin significantly contribute to its therapeutic profile, particularly in cancer prevention and cardiovascular health. In this regard, key regulatory mechanisms include modulation of pathways such as NF-κB, Wnt/β-catenin, mTORC1, and epigenetic modifications, such as histone methylation. Gaining a deep insight into the multifaceted molecular mechanisms of aspirin is of considerable importance for harnessing its full potential in clinical applications. Overview of molecular mechanism of aspirin in cancer are shown in Figure 3.

COX-Dependent Mechanism of Aspirin

Aspirin, a widely used non-steroidal anti-inflammatory drug (NSAID),⁶⁵ plays an impressive role as a cancer-targeting therapeutic intervention through its cyclooxygenase (COX)-dependent mechanism.⁶ This mechanism primarily involves the irreversible inhibition of COX enzymes,¹ particularly COX-1 and COX-2,⁶⁶ by introducing the acetylation of a specific serine residue (Ser530) in their active sites.⁶⁷ This acetylation enables permanent loss of enzymatic activity, leading to reduced production of prostaglandins and other mediators derived from arachidonic acid. In the physiological conditions, COX-1 is normally produced and involved in gastric protection and platelet aggregation.⁶⁸ However, COX-2 is induced during inflammatory responses and is frequently upregulated in various tumors.^{69,70} Aspirin's selective inhibition of COX-2 over COX-1 in cancer is advantageous, as it decreases the production of tumor-promoting prostaglandins, while sparing COX-1-dependent physiological processes. One of the most important consequences of

Table 2 Overview of Aspirin Based Nanotechnological Formulation for Cancer Therapy

Study	Nanotechnology	Cancer Type	Mechanism of Action	Advantages
Gal-PDA-MSN@Asp	Galactosamine-modified polydopamine-coated mesoporous silica nanoparticles	Liver cancer	Targeted delivery; pH-sensitive drug release	Controlled release; increased efficacy
Asp/TLs	Thermo-responsive liposomes	Triple-negative breast cancer	Temperature-triggered drug release; gene regulation	Targeted therapy; reduced dosage; enhanced cytotoxicity
P3C-Asp	Dextran-aspirin nanomedicine	Colorectal cancer	Releases salicylic acid; scavenges ROS; modulates gut microbiota	Immune regulation; gut inflammation modulation
Asp@cLANVs	Cross-linked lipoic acid nanovesicles	Postsurgical cancer recurrence	Combines cancer cell eradication and microenvironment modulation	Synergistic effects; alleviates surgery-induced inflammation
CUR&ASP	Chondroitin sulfate-glycyrrhetic acid liposomes	Hepatocellular carcinoma	Targets cancer cells and platelets	Dual targeting; potent anti-cancer effects
Quercetin-Aspirin Nanoparticles	Eudragit L100-coated chitosan nanoparticles	Colorectal cancer	Targeted delivery; synergy between quercetin and aspirin	Synergistic effects; improved stability
Theranostic Platform for IFN	Structure-switching aptamer biosensor	Cytokine-related inflammation	Cytokine-guided drug delivery; on-demand local delivery	Personalized therapy; reduced systemic side effects
TAFL	Exosome fusion liposomes with aspirin and photothermal agents	Cancer stem cell-mediated recurrence	Photothermal therapy; DNA damage; reduces CSC stemness	Improved safety; enhanced therapy outcomes
Thiolated NPs	Thiolated disulfide-bridged nanoparticles	Colorectal cancer	Inhibits epithelial-mesenchymal transition (EMT)	Improved efficacy and stability; non-cytotoxic drugs
Nanoamorphous Exosomal Platform	Nanoamorphous exosomal platform	Breast and colorectal cancer	Homing effect to parental cancer cells	Enhanced anticancer efficacy; potential for clinical use
MNP-Asp-PD-PG-F	Mesoporous silica nanoparticles with folic acid targeting	Breast cancer	Targeted delivery to cancer cells	Increased efficacy; reduced side effects
Nano-encapsulated FA & ASP	Ferulic acid and aspirin nanocombinations	Pancreatic cancer	Synergistic inhibition of cancer pathways	Enhanced chemopreventive effects; lower required dosages
ASP SLNs + Curcumin/SF	Solid lipid nanoparticles	Pancreatic cancer	Combines multiple agents for synergistic effect	Improved chemoprevention; controlled release
Nano-Aspirin in Breast Cancer	Nanotechnology for DNA repair and gene regulation	Breast cancer	Enhanced DNA repair capacity; gene regulation	Enhanced safety and efficacy
BSA-NPs	Bovine serum albumin nanoparticles	Metastatic cancer	Inhibition of metastasis-related proteins	Effective anti-metastatic therapy
FA-BSA@DA	FA-BSA@DA platform	Breast cancer	Inhibits heparanase; prevents metastasis	Prevents recurrence and metastasis
HS-ASP & PTX	Hydrogen sulfide-releasing aspirin with paclitaxel	Lung cancer	Sensitizes cancer cells to chemotherapy; controlled release	Improved treatment efficacy; reduced drug resistance
ACS c-SLNs	Chitosan-solid lipid nanoparticles	Pancreatic cancer	Overcomes hydrophobicity; improved therapeutic efficacy	Safe for long-term use; potential for chemoprevention
PLGA Nanoparticles	PLGA nanoparticles	Colorectal cancer	Synergistic chemopreventive effects; targeted delivery	Enhanced efficacy; controlled drug release
TiO ₂ Nanocomposites	Polypyrrole-coated mesoporous TiO ₂	Cancer metastasis	Photothermal and sonodynamic therapy; controlled release	Combats metastasis and recurrence; synergistic therapy
mPEG-PLGA NPs	mPEG-PLGA nanoparticles	Ovarian cancer	Overcomes hydrophobicity; enhanced therapeutic efficacy	Potential clinical benefits; improved drug solubility

(Continued)

Table 2 (Continued).

Study	Nanotechnology	Cancer Type	Mechanism of Action	Advantages
ASP Nanoparticles	Aspirin nanoparticles for DNA protection	Lung cancer	Enhanced DNA repair; anti-inflammatory effects	Targeted therapy; reduced side effects
Exosomal Delivery Systems	Poloxamer-based nanostructured exosomes	Breast and colorectal cancer	Improved solubility; targeted delivery	Potent anticancer agent; potential for clinical translation
c-SLNs for PDAC	Chitosan-coated solid lipid nanoparticles	Pancreatic cancer	Synergistic chemoprevention; controlled release	Effective at low doses; safe for long-term use
Apt/UD NPs	Aptamer-functionalized nanoparticles	Ovarian cancer	Aptamer-mediated targeting; combined drug therapy	Promising approach for cancer therapy

COX-2 inhibition by aspirin is the reduction in prostaglandin E2 (PGE2) levels.⁷¹ PGE2 is a key pro-inflammatory mediator that promotes cancer progression through several mechanisms.⁷² It activates signaling pathways such as PI3K/Akt and MAPK, which drive cancer cell proliferation and survival.⁷³ Hence, thereby by suppressing PGE2 synthesis, aspirin inhibits these pathways, leading to reduced cancer cell growth. Additionally, COX-2-derived prostaglandins, including PGE2, stimulate the production of vascular endothelial growth factor (VEGF), a critical factor for angiogenesis—the formation of new blood vessels that supply tumors with nutrients⁷⁴ is considerably important for Cox dependent mechanism of aspirin in cancer. Aspirin inhibits this angiogenic switch, ultimately limiting tumor vascularization. Moreover, prostaglandins also enhance tumor cell invasiveness by triggering epithelial-to-mesenchymal transition (EMT), a key step in metastasis⁷⁵ aspirin has the efficacy to differentially target this pathway. To address this, the Aspirin-mediated lowering of prostaglandin levels may reduce the metastatic potential of cancer cells.⁷¹ Aspirin's COX-dependent actions extend beyond direct tumor effects to modulate the immune system.⁶ Usually, elevated levels of COX-2 and PGE2 within the tumor microenvironment suppress the activity of immune cells, such as cytotoxic T lymphocytes and natural killer cells,⁷⁶ which are essential for anti-tumor immunity⁷⁷ and these are the key molecular targets of aspirin. Therefore, by inhibiting COX-2 and reducing PGE2 levels, aspirin can enhance immune surveillance and bolster the body ability to mount an effective anti-tumor response.⁷⁸ Furthermore, Aspirin capability to inhibit COX-2 and reduce chronic inflammation has important clinical implications⁷⁹ and can be further explored for inflammatory related cancer. It is reported that regular intake of aspirin has been associated with a reduced incidence of several cancers, particularly colorectal cancer, by decreasing the levels of PGE2 this ensures further efficacy of aspirin in cancer treatment. Furthermore, aspirin may act synergistically with other cancer therapies, improving the efficacy of chemotherapeutic agents by modulating the inflammatory tumor microenvironment and reducing adverse effects.

COX-Independent Mechanism of Aspirin

Aspirin is a multi-potent drug capable of exerting its therapeutic effects in the COX-independent mechanisms as well. It modulates fine regulation of multiple cellular pathways. In turn, this contributes significantly to aspirin's therapeutic benefits, particularly against inflammation and cancer interventions.

NF-κB

Aspirin substantially influences the NF-κB signaling pathway,⁸⁰ a critical regulator of inflammation, cell survival, and apoptosis. These effects of Aspirin make it a valuable agent in cancer chemoprevention, particularly in cancer.^{81,82} For influencing this pathway, upon interaction with cell membrane receptors, Aspirin activates receptor-interacting protein kinases (RIPK), which initiates a cascade involving the TAK1/TAB complex. Then, this complex phosphorylates the IκB kinase (IKK) complex.⁸³ Consequently, this leads to the degradation of IκB proteins, allowing NF-κB dimers, primarily p65/p50, to translocate into the nucleus.⁸³ Once inside nucleus, these dimers activate transcription of genes responsible for apoptosis and cell survival, shifting the balance in favor of cell death. By simultaneously promoting the expression of pro-apoptotic genes and repressing anti-apoptotic pathways, Aspirin enhances apoptosis in neoplastic cells.⁸⁴

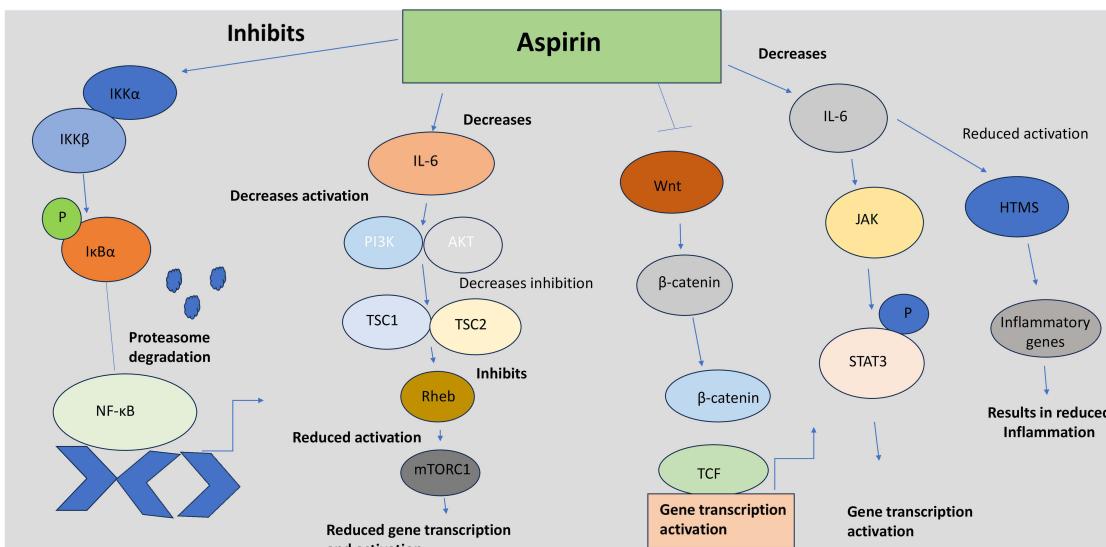
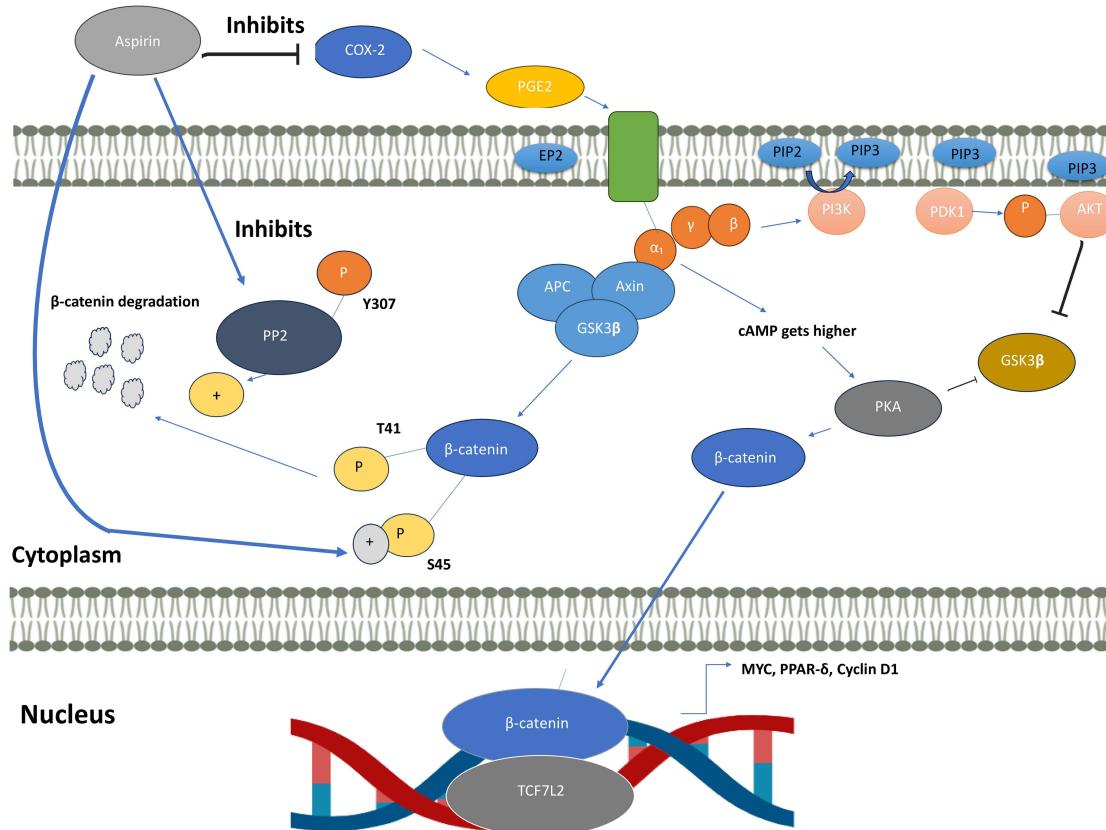


Figure 3 Overview of molecular mechanism of aspirin in cancer. Aspirin directly inhibits cyclooxygenase-2 (COX-2), a key enzyme involved in the production of prostaglandins. This inhibition leads to a decrease in prostaglandin E2 (PGE2) production. Lower PGE2 levels suppress pro-tumorigenic signaling pathways such as PI3K/AKT and NF-κB. This suppression ultimately inhibits cancer cell proliferation, invasion, and metastasis. Aspirin elevates intracellular cyclic adenosine monophosphate levels. Increased cAMP activates protein kinase A (PKA). PKA inhibits glycogen synthase kinase 3β (GSK3β). GSK3β inhibition leads to the stabilization of β-catenin. Stabilized β-catenin translocates to the nucleus. β-catenin activates the transcription of genes involved in cell proliferation and survival. Aspirin can directly inhibit IKK, preventing the phosphorylation and degradation of IκB. Janus kinases (JAKs) associated with the receptor become activated due to aspirin. Activated JAKs phosphorylate STAT3 protein on specific tyrosine residues. In the nucleus, STAT3 dimers bind to specific DNA sequences and activate the transcription of target genes involved in cell proliferation, survival, and inflammation. Aspirin, through its inhibition of COX-2, leads to a reduction in pro-inflammatory cytokines like IL-6. This decrease in inflammatory signaling attenuates the activation of the PI3K/AKT pathway. The subsequent reduction in PI3K/AKT signaling leads to the activation of the TSC1/TSC2 complex, which in turn inhibits Rheb. The inhibition of Rheb results in decreased mTORC1 activity, ultimately leading to reduced protein synthesis and cell growth.

Wnt/B-Catenin Signaling Pathway

Aspirin-mediated modulation of Wnt signaling pathway has marked impacts on cancer biology, particularly involving transcriptional regulation of key proteins that affect gene expression and cell behavior.⁸⁵ In this regard, the canonical Wnt pathway gets initiated when Wnt proteins bind to Frizzled⁸⁶ receptors, leading to the recruitment of Dishevelled (Dsh) protein, which ultimately stabilizes β -catenin. This enables the cytosolic accumulation of β -catenin, and promotes its nuclear translocation. Once inside the nucleus, it acts as a coactivator for TCF/LEF transcription factors.⁸⁷ However, aspirin disrupts the normal degradation of β -catenin by interfering with the destruction complex, including Axin, APC, GSK3, and PP2A.⁸⁸ Specifically, Aspirin interferes with PP2A activity, which ultimately alters Wnt signaling leading to dysregulated target gene expression.⁸⁹ As a result, the transcription of genes promoting cell proliferation and survival is inhibited, while apoptosis-related genes may be upregulated. Furthermore, aspirin increases the expression of Dickkopf-1 (Dkk-1), a potent antagonist of Wnt signaling, thereby elevating its inhibitory effect on the pathway.⁹⁰ Overall, aspirin ability to influence the Wnt signaling pathway assists in inhibiting tumorigenesis by supporting the degradation of β -catenin and suppressing proliferative signals in cancer cells and further research is needed to validate this pathway.

STAT3 Pathway

STAT3 is an important pathway affected by anti-cancer drug for cancer treatment. Aspirin significantly impacts key cellular processes such as proliferation, apoptosis, and immune response by influencing the STAT3 signaling pathway.⁹¹ The pathway is initiated when cytokines, such as interleukin-6 (IL-6) bind to their receptors. Aspirin leads to reduction in the levels of IL-6. This binding activates Janus kinases (JAKs), which phosphorylate STAT3. This phosphorylation allows STAT3 to dimerize and translocate to the nucleus, where it promotes the transcription of its target genes involved in cell growth and survival.⁹² However, Aspirin interferes with this pathway by activating protein phosphatase 2A (PP2A). PP2A dephosphorylates STAT3, reducing its phosphorylation and signaling activity.⁹³ This dephosphorylation impairs STAT3 nuclear translocation, diminishing its ability to activate transcription, ultimately suppressing the expression of proliferation-related genes, such as Mcl-1⁹⁴ and it leads to a reduction in cancer growth and development. Overall, aspirin modulation of the STAT3 pathway highlights its potential to inhibit cancer cell growth and enhance apoptosis, offering therapeutic benefits in managing cancer and inflammation and it paves the way for further targeting of STAT3 as a molecular target for cancer inhibition.

mTORC1 Pathway

mTOR is another key molecular pathway disrupted in lot of cancers. Aspirin significantly impacts the mTOR (mechanistic target of rapamycin) signaling pathway,⁹⁵ a pathway central to regulating cell growth, proliferation, and metabolism. This pathway involves two complexes, mTORC1 and mTORC2⁹⁶ these two key molecular targets are the foremost target of aspirin. These complexes respond to signals like growth factors and nutrients, such as insulin, which activates mTORC1 through the PI3K/Akt pathway, promoting cellular growth.⁹⁷ However, aspirin modulates this pathway by activating AMP-activated protein kinase (AMPK), which inhibits mTORC1 via phosphorylation of a negative regulator of this pathway, TSC2.^{98–100} This leads to reduced protein synthesis and increased autophagy, essential for cellular maintenance. Although, aspirin's activation of AMPK can inhibit mTORC1 and thus inhibit cell growth, its parallel activation of mTORC2 and subsequent increase in MCL-1 may offset some of aspirin's anticancer effects. Therefore, using aspirin alongside MCL-1 inhibitors could help counteract this effect, potentially enhancing the anticancer efficacy of aspirin by limiting cancer cell survival mechanisms.⁹² To reinforce this finding, a study involving CRC cells demonstrated that administration of aspirin reduced mTOR signaling by inhibiting the mTOR effectors S6K1 and 4E-BP1 along with modulation of the nucleotide ratios and activated AMPK in these cells. Further In vivo analysis validated similar kind of results, where the rectal mucosa of these patients was found to harbor a reduced phosphorylation of S6K1 and S6¹⁰⁰ these indicates the potential of aspirin in treating cancer on a broad level. Overall, aspirin modulation of the mTOR pathway impacts key processes like cell growth, autophagy, and metabolism, highlighting its therapeutic potential and evokes a path for further research.

Histone Methylation Pathway

Targeting cancer on a molecular level is a focus of recent studies histone methylation is one of the key modifications disrupted in cancer. Aspirin significantly affects the histone methylation pathway (Xiaoyuan Zhang et al, 2020), which plays a critical role in regulating gene expression and chromatin structure. Aspirin exhibits its histone methylation tendency by influencing key molecular proteins, such as histone methyltransferases (HMTs),¹⁰¹ sirtuins, and DNA methyltransferases (DNMTs).¹⁰² In this regard, histone methylation, mediated by HMTs like SETD2 and EZH2, can either activate or repress gene expression depending on the precise residues modified (eg, H3K4, H3K27).¹⁰³ However, Aspirin shows a great potential as it alters histone methylation levels and influences the specifically modified residues, ultimately impacting genes involved in inflammation and cancer progression.¹⁰¹ Furthermore, Aspirin inhibits mitochondrial function, leading to increased ROS production as an outcome of disruption in histone methylation. In turn, ROS activates signaling pathways that regulate histone methyltransferases, resulting in decreased H3K4 methylation and subsequent suppression of VEGF gene expression.¹⁰⁴ In conclusion, aspirin-mediated modulation of critical molecular proteins in the histone methylation pathway highlights its potential as an anti-cancer agent, leveraging epigenetic mechanisms to influence gene expression and improve therapeutic outcomes further evaluation is needed to confirm these outcomes for future proceedings.

Aspirin and Cancer

Aspirin offers remarkable anti-cancer potential against multiple cancer types. Many studies have reported precise signaling pathways affected and key outcomes of aspirin treatment in cancer. Precisely, it has shown marked effects in actively combating colon cancer, melanoma, lung cancer,¹⁰⁵ ovarian cancer, pancreatic cancer, liver cancer, and several other cancers, including breast cancer, prostate cancer, leiomyoma, glioblastoma, and oral squamous cell carcinoma. Figure 4 illustrates the diverse cancer-related pathways modulated by aspirin, emphasizing its role as a multi-targeted therapeutic agent in various cancer types.

Aspirin and Colon Cancer

Recent research continues to highlight the potential of aspirin in preventing and treating colorectal cancer (CRC). Studies indicate that aspirin can induce G1 cell cycle arrest and apoptosis in CRC cells through the modulation of the p53–CDK1 pathway, where p53 is upregulated and CDK1 is downregulated, contributing to its anticancer effects.¹⁰⁶ Regular aspirin use has been associated with a significant reduction in the 10-year cumulative incidence of CRC, with the greatest benefit observed in individuals with less healthy lifestyle scores, highlighting aspirin's role as a chemopreventive agent for CRC.¹⁰⁷ Additionally, aspirin's anticancer effects are enhanced when combined with other compounds, such as oleanolic acid, which inhibits CRC cell proliferation and invasion, induces S-phase arrest, and promotes apoptosis through the Akt/NF κ B/I κ B α /COX2 pathway.¹⁰⁸ The combination of aspirin and zinc has been shown to reduce inflammation and tumor progression in colitis-associated colorectal cancer in mice, improving markers such as PCNA and STAT3, while also enhancing antioxidant defenses like Nrf-2, catalase, and SOD.¹⁰⁹ Further studies in FAP model Min mice suggest that aspirin inhibits intestinal tumorigenesis by regulating β -catenin signaling, oxidative stress, and inflammation, while reactive carbonyl species serve as biomarkers for clinical trials.¹¹⁰ Additionally, aspirin combined with genistein (GEN) demonstrated dose-dependent cytotoxic effects on HCT-116 colorectal cancer cells by inhibiting cell migration and altering cell morphology. The combination also showed antiangiogenic effects in the CAM model by disrupting the vascular network.¹¹¹ Aspirin has also been found to reduce circulating tumor DNA levels and increase bone tissue density in metastatic colorectal cancer patients with osteoporosis, activating the PI3K/Akt signaling pathway and enhancing osteoblast proliferation.¹¹²

In combination with dipyridamole, aspirin has demonstrated superior anticancer effects against CRC in mouse models and in vitro. This synergy is driven by ER stress and a pro-apoptotic unfolded protein response, indicating the potential for adjuvant therapies in CRC.¹¹³ Moreover, aspirin has been shown to suppress TIGIT expression on T cells and Tregs, enhancing effector T cell function and improving immune responses against CRC progression.¹¹⁴ Aspirin modulates gut microbiota composition, particularly reducing *Enterococcus cecorum*, thereby enhancing immune responses by

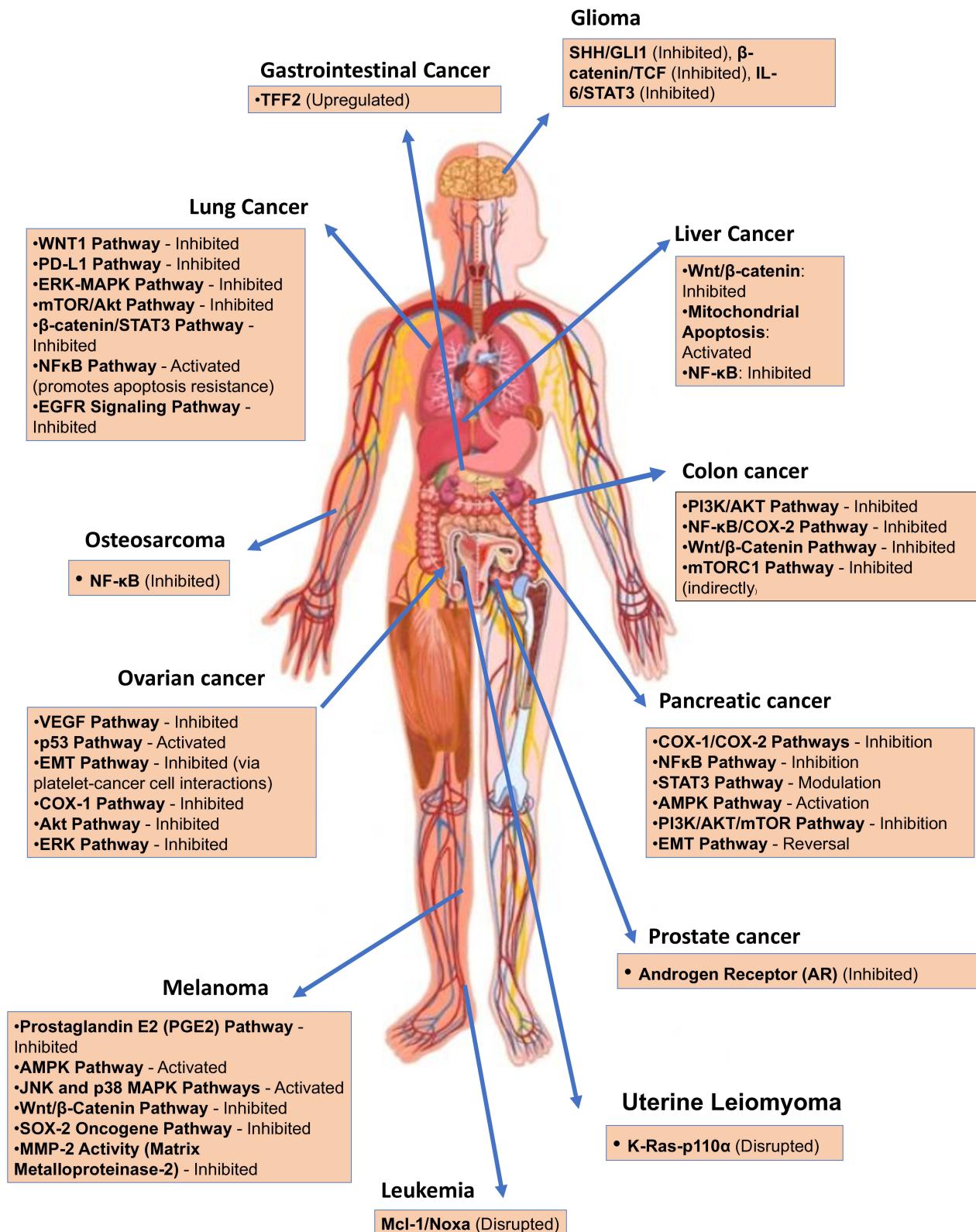


Figure 4 Targeted Cancer Pathways Modulated by Aspirin Across Various Cancer Types. This figure depicts the pathways targeted by aspirin in different cancer types. The schematic human body highlights cancer sites and the associated molecular pathways affected by aspirin. These include inhibition of pathways such as WNT1, PD-L1, NF- κ B, and COX-2, among others, across cancers like lung, colon, liver, ovarian, and pancreatic cancer. Aspirin also disrupts key signaling pathways like mTOR/Akt, PI3K/AKT, β -catenin, and promotes tumor-suppressive mechanisms such as mitochondrial apoptosis and p53 pathway activation.

decreasing Treg cell functionality and promoting CD8+ T cells, Th17 cells, and B cells.¹¹⁵ Recent studies highlight that metformin and aspirin have significant antiproliferative, cytotoxic, and antimigratory effects on PIK3CA-mutant HT-29 CRC cells, presenting a promising treatment option for this genetic subtype of CRC.¹¹⁶ Aspirin has also demonstrated synergistic effects with cisplatin, enhancing its efficacy by inhibiting cell proliferation, migration, and invasion, as well as inducing apoptosis through the PI3K/Akt, NF-κB/COX-2, and Bcl-2 signaling pathways.¹¹⁷ Moreover, aspirin induces immunogenic cell death in colon cancer cells, characterized by the expression of calreticulin (CRT) and HSP70, alongside activation of endoplasmic reticulum (ER) stress and glycolytic changes, which could be leveraged in combination with immune checkpoint inhibitors like anti-PD-1 and anti-CTLA-4.¹¹⁸

Aspirin's role in regulating specialized proresolving mediators (SPMs) in colonic tissues has been emphasized, with aspirin downregulating PD-1 expression in macrophages and CD8+ T cells, thus improving immune responses against inflammation-associated CRC.¹¹⁹ Moreover, aspirin has been found to reduce CRC incidence by inhibiting specificity proteins (Sp1, Sp3, Sp4), key transcription factors involved in cancer progression. This mechanism also correlates with improved immune responses and survival rates in CRC patients.¹²⁰ The active metabolite salicylate has been proposed to contribute to aspirin's anticancer effects, further supporting the need for continued research into its mechanisms.¹²¹ Recent studies have also explored combination therapies involving aspirin, such as its pairing with γ-tocopherol (γT) to reduce tumor size and multiplicity in a colitis-associated cancer (CAC) model, while mitigating aspirin-induced gastric lesions and altering the gut microbiota. This combination also suppressed HCT116 CRC cell growth, suggesting a novel chemopreventive strategy.¹²² Further investigations into aspirin's impact on Wnt signaling in colon cancer stem cells (CCSCs) and adenoma formation in APCmin/+ mice showed that aspirin, when combined with DT3, inhibited growth and induced apoptosis in CCSCs, while minimally affecting normal colon cells.¹⁰

Aspirin has also been demonstrated to counter chemoresistance in CRC. For instance, it inhibits the growth of stem-like colon cancer cells, reducing resistance to regorafenib by downregulating CD133, CD44, and CD24 markers while upregulating CDX2 and PTEN.¹²³ Additionally, aspirin has been shown to significantly reduce tumor development in APCmin/+ mice and azoxymethane-treated models, underscoring its role in microbiota-dependent CRC prevention.¹²⁴ Recent research has also emphasized aspirin's efficacy in PIK3CA-mutant cancers, where it has improved survival outcomes in CRC patients with PIK3CA mutations, suggesting aspirin's potential in precision medicine.¹²⁵ In a novel approach, aspirin has been found to exert antibiotic effects against the oncomicrobe *Fusobacterium nucleatum*, which is implicated in CRC development. This was evidenced by aspirin's ability to inhibit bacterial growth, both in actively growing and stationary strains.¹²⁶ Moreover, aspirin inhibits epithelial-mesenchymal transition (EMT) in SW480 tumor cells by repressing the expression of key regulators of EMT and Wnt signaling, further highlighting its potential to target critical cancer-related pathways.¹²⁷ A recent study also found that aspirin blocks cyclooxygenase metabolism, reducing pro-inflammatory cytokines and inhibiting Wnt signaling, particularly through the suppression of WNT6 via NR4A2 transcription factor.¹²⁸ This finding suggests aspirin's promise in inflammatory-related colon cancer treatment. Lastly, a liquid formulation of aspirin, IP1867B, has been reported to exhibit differential effects on TXB2 generation and cyclooxygenase isozymes, showing greater potency in inhibiting TXB2 production compared to standard aspirin. This differential effect could hold promise for advancing aspirin's role in cancer therapy, particularly in targeting TXB2, a key component in inflammation and tumor progression.¹²⁹ Furthermore, NO-ASA, a nitric oxide-releasing aspirin derivative, has been shown to be significantly more effective than traditional aspirin in inhibiting colon cancer cell growth. Its mechanism involves the depletion of glutathione, oxidative stress induction, and apoptosis activation, alongside the disruption of adherens junctions and inhibition of Wnt signaling, reinforcing its chemopreventive properties and suggesting a more effective approach for colon cancer therapy.¹³⁰

Aspirin and Melanoma

A growing body of evidence highlights the potential of aspirin as a therapeutic agent for melanoma, demonstrating its effectiveness in various settings, both as a monotherapy and in combination with other treatments. Several studies suggest that chronic aspirin use may reduce the risk of melanoma, with recent research exploring aspirin's combination with other compounds for enhanced anti-melanoma activity. For example, aspirin combined with fisetin (ASA + FIS) exhibits significant synergistic effects, reducing cell viability and inducing apoptotic-like nuclear changes in A375 melanoma cells. The combination also inhibited angiogenesis in vivo, without showing irritant effects on the chorioallantoic membrane, positioning

ASA + FIS as a promising combinatorial therapy for malignant melanoma.¹³¹ Mechanistically, aspirin has been shown to suppress prostaglandin E2 (PGE2) levels and activate AMP-activated protein kinase (AMPK), which plays a role in the inhibition of melanoma cell growth. Additionally, aspirin can regulate Wnt signaling by downregulating LDL receptor-related protein-6 and β-catenin, both key players in melanoma cell proliferation and survival.¹³² Aspirin has also demonstrated the ability to inhibit the survival of B16 melanoma cells, inducing apoptosis through increased caspase 3/7 activity. Notably, aspirin's effects on murine B16 melanoma tumors were independent of cellular and stromal PAF-R expression, suggesting a PAF-R-independent mechanism in its anticancer activity.¹³³ In vitro studies have further shown aspirin's ability to suppress B16 melanoma cell proliferation through the activation of JNK and p38 mitogen-activated protein kinases. When administered at plasma-attainable and nontoxic levels, aspirin induced the activation of these kinases, with JNK inhibition leading to diminished anti-proliferative effects. Aspirin also demonstrated synergistic effects with BCNU, a chemotherapy drug, enhancing B16 melanoma cell death.¹³⁴

Aspirin's anticancer effects are not limited to apoptosis. It has also been reported to inhibit melanoma cell motility, colony formation, and pigmentation at specific concentrations, further supporting its antineoplastic potential.¹³⁵ In a murine model, aspirin treatment inhibited tumor growth by 50% at 150 mg/kg for 13 days, showcasing its potential as an effective therapeutic agent for melanoma.¹³⁶ A notable clinical study investigated the combination of high-dose aspirin with pembrolizumab and ipilimumab in patients with advanced melanoma, showing a promising objective response rate of 62.9%. These findings underscore aspirin's potential as an adjunct to immune checkpoint inhibitors in melanoma therapy.¹³⁷ In addition, aspirin combined with indole-3-carbinol has exhibited significant antiproliferative effects on melanoma cells with oncogenic BRAF mutations. This combination induced a G1 cell cycle arrest and reduced MITF-M expression by disrupting its promoter activity, which is crucial for melanocyte regulation.¹³⁸ Aspirin also inhibits matrix metalloproteinase-2 (MMP-2) activity, which is associated with the metastasis of B16 melanoma cells. In vivo, aspirin reduced the metastasis of B16F0 cells in C57BL/6J mice by 44%, indicating its potential in combating melanoma metastasis.¹³⁹

Furthermore, aspirin may help overcome immune checkpoint resistance. In a study using anti-PD-1 immune checkpoint inhibitors, aspirin increased the proportion of PD-1+ CD8+ T-cells within the tumor microenvironment (TME), suggesting a potential role in modulating T-cell responses in melanoma.¹⁴⁰ Aspirin has also been shown to induce non-apoptotic cell death in human melanoma cells by disrupting the mitochondrial network and increasing mitochondrial Ca²⁺ levels and reactive oxygen species (ROS). These effects were independent of COX inhibition, highlighting aspirin's broader anticancer potential. Interestingly, aspirin sensitized melanoma cells to TRAIL-induced apoptosis in a caspase-dependent manner, suggesting that combining aspirin with TRAIL therapy could be a promising strategy for melanoma treatment.^{141,142} In conclusion, aspirin shows strong promise as a melanoma therapeutic agent, particularly when used in combination with other drugs or immune therapies. The ongoing research into aspirin's molecular mechanisms and its potential in combination therapies will further clarify its role in melanoma treatment and prevention.

Aspirin and Lung Cancer

Aspirin demonstrates impressive therapeutic potential against lung cancer by targeting various mechanisms that contribute to tumor growth, metastasis, and drug resistance. A study explored the role of blood-brain barrier (BBB) permeability in lung cancer brain metastasis and found that aspirin administration increased the expression of tight junction proteins (HSP70, ZO-1, and occludin), reducing BBB permeability and potentially inhibiting brain metastasis. However, TNF-α reversed these effects, suggesting a modulatory influence on aspirin's protective role against metastasis.¹⁴³ Further research investigated the triple therapy of aspirin, afatinib, and vinorelbine in treating p53 wild-type nonsmall cell lung cancer (NSCLC) cells. The combination synergistically inhibited cell proliferation and induced apoptosis more effectively than the individual agents, with mechanistic analysis revealing the inactivation of the EGFR/AKT/mTOR pathway, an increase in p53 levels, and enhanced mitochondrial dysfunction, offering a promising treatment strategy for p53 wild-type NSCLC patients.¹⁴⁴ Additionally, a novel acetylated derivative of Undaria pinnatifida fucoidan (ASA-UPFUC) was developed, which inhibited A549 lung cancer cell proliferation in a dose-dependent manner, induced apoptosis through the mitochondrial pathway, and enhanced biological activity, showing promise for lung cancer chemoprevention.¹⁴⁵ Another study highlighted how aspirin inhibited metastasis in a murine model of lung cancer by

preventing neutrophil recruitment, a finding particularly relevant in the context of postoperative pneumonia in esophageal cancer patients, which increases lung metastasis.¹⁴⁶

Aspirin's efficacy in targeting the TAZ/PD-L1 axis is significant, as it suppresses PD-L1 expression at both mRNA and protein levels by inactivating the PD-L1 promoter through TAZ. Overexpression of PD-L1 reversed aspirin's growth-inhibitory effects, suggesting that aspirin could be a valuable therapeutic agent for enhancing immune responses in lung cancer therapy.¹⁴⁷ Moreover, aspirin combined with low-dose celecoxib exhibited synergistic anticancer effects by enhancing apoptosis via caspase-9/caspase-3 activation, inducing ER stress through GRP78 inhibition, and suppressing migration via MMP-9/MMP-2 downregulation. This combination also inhibited ERK-MAPK signaling, offering superior tumor growth suppression *in vivo* compared to either drug alone.¹⁴⁸ When combined with osimertinib, aspirin significantly improved progression-free survival (PFS) and overall survival (OS) in patients with EGFR-mutant NSCLC, even in those with central nervous system metastases. These findings suggest that aspirin may enhance osimertinib efficacy and provide a promising strategy to improve clinical outcomes in NSCLC.¹⁴⁹ Furthermore, daily aspirin use in combination with PD-L1 inhibitors in NSCLC patients showed a trend toward improved complete remission rates and significantly reduced the likelihood of progressive disease, suggesting that aspirin could enhance outcomes in combination with PD-L1 inhibitors.¹⁵⁰ Interestingly, aspirin exhibits a dual role in cancer cell proliferation. At low concentrations, aspirin promotes growth by activating the MAPK signaling pathway, while higher doses inhibit proliferation. This dose-dependent effect underscores aspirin's potential for modulating cancer cell behavior in lung cancer treatment.¹⁵¹ Additionally, aspirin-triggered resolvin D1 (AT-RvD1), a product of ALOX5 biosynthesis, resolves inflammation and exhibits anticancer properties by promoting macrophage-mediated tumor clearance in a KrasG12D lung adenocarcinoma model. AT-RvD1 reduced tumor growth and improved the tumor immune landscape, highlighting its potential efficacy in lung cancer therapy.¹⁵² Aspirin also inhibits aerobic glycolysis and proliferation in NSCLC by targeting the AMPK/SIRT3/HK-II pathway. This leads to mitochondrial dysfunction, reduced glycolytic activity, and hexokinase-II release from mitochondria, further supporting aspirin's role in targeting lung cancer metabolism for chemoprevention.¹⁵³

Aspirin has shown promise in overcoming drug resistance, as demonstrated by its ability to enhance the antitumor efficacy of osimertinib in osimertinib-resistant NSCLC. Aspirin promotes Bim-dependent apoptosis by inhibiting Akt/FoxO3a signaling, significantly reducing tumor growth in xenograft models and extending PFS in clinical patients.¹⁵⁴ Aspirin has also been shown to modulate the miR-98/WNT1 axis, suppressing the target gene WNT1 and inhibiting lung cancer cell viability and colony formation, providing a novel mechanistic explanation for its antineoplastic effects.¹⁵⁵ Additionally, aspirin inhibits metastasis in Lewis lung carcinoma cells and acts as a negative regulator of epithelial-to-mesenchymal transition (EMT) in oncogenic K-RAS-expressing NSCLC cells by downregulating Slug and upregulating E-cadherin. This effect is mediated by the activation and nuclear translocation of p65NF κ B, crucial for Slug transcription, which ultimately inhibits cancer proliferation.¹⁵⁶ In vivo studies have also shown that aspirin reduces angiogenesis, decreasing VEGF expression and vascular density in A549 xenografts, suggesting its role in tumor growth suppression and angiogenesis inhibition in NSCLC.¹⁵⁷ Furthermore, aspirin has been reported to suppress PD-L1 expression, a key target in cancer therapies, by inactivating the PD-L1 promoter through TAZ. This inhibition of PD-L1 contributes to enhanced tumor growth suppression.¹⁴⁷ Additionally, aspirin modulates exosomal contents such as miR-135b and miR-210, suppressing hypoxia-induced exosomal release in NSCLC, which may contribute to an improved tumor microenvironment and response to therapy.¹⁵⁸ In combination with other agents, aspirin has shown promising effects. The acetylated derivative ASA-UPFUC, synthesized with aspirin, demonstrated significant antitumor activity, enhancing solubility and biological activity and potentially serving as a dietary additive for lung cancer chemoprevention.¹⁴⁵ Similarly, NO-Aspirin, an aspirin derivative, reduced tumor size and number in a lung cancer model, further emphasizing aspirin's potential in cancer treatment.¹⁵⁹

Aspirin has also been explored as an adjuvant therapy in overcoming chemotherapy resistance. For instance, aspirin has been shown to enhance cisplatin sensitivity in cisplatin-resistant NSCLC cells by inhibiting stemness factors and modulating key signaling pathways such as mTOR/Akt, thereby reducing cell survival and improving treatment outcomes.¹⁶⁰ The combination of aspirin and cisplatin has been found to inhibit migration in cancer stem cell-enriched NSCLC spheroids by repressing mTOR gene transcription and deactivating Akt, Snail, and β -catenin, ultimately enhancing cisplatin's antitumor efficacy.¹⁶¹ The combination of aspirin with decitabine has also demonstrated significant

suppression of NSCLC cell growth and migration via inhibition of the β -catenin/STAT3 signaling pathway.¹⁶² Moreover, aspirin has been reported to reverse the effects of methotrexate (MTX) by alleviating S-phase accumulation and promoting cell cycle recovery, which may be important in overcoming MTX-induced chemoresistance.¹⁶³ When combined with Troglitazone (TGZ), aspirin enhanced growth inhibition and apoptosis in lung cancer cells, highlighting its potential as a therapeutic adjunct in combination with other agents.¹⁶⁴ Finally, aspirin combined with erlotinib showed significant anti-proliferative and anti-metastatic effects in NSCLC, activating E-cadherin and suppressing the p38 MAPK pathway, providing further evidence of its potential in combination therapies.¹⁶⁵ In conclusion, aspirin's multifaceted effects on tumor progression, metastasis, and drug resistance make it a promising candidate for combination therapy in lung cancer. While it holds significant potential, its dose-dependent effects and possible activation of NF κ B pathways,¹⁶⁶ leading to apoptosis resistance, highlight the need for careful dose optimization in clinical settings.¹³⁸

Aspirin and Ovarian Cancer

Aspirin demonstrates promising therapeutic potential in ovarian cancer through various mechanisms. A combination of recombinant human apurinic/apyrimidinic endonuclease 1/redox factor 1 (rhAPE1/Ref-1) and aspirin synergistically induces cell death and apoptosis in ovarian cancer cells, particularly PEO14, and enhances paclitaxel-induced apoptosis, suggesting a novel approach to improving treatment outcomes.¹⁶⁷ Aspirin also downregulates PD-L1 expression and suppresses the PD-1/PD-L1 immune checkpoint, both *in vitro* and *in vivo*. This reduction in PD-L1 levels, combined with enhanced efficacy of anti-PD-L1 therapy, positions aspirin as a promising adjuvant in ovarian cancer immunotherapy.¹⁶⁸ Additionally, when combined with cisplatin, aspirin significantly inhibits tumor growth and induces apoptosis in epithelial ovarian cancer (EOC) cells, enhancing p53 acetylation and activating p53 target genes like CDKN1A, BAX, and PUMA.¹⁶⁹

A novel aspirin derivative, Aspirin-PC, shows superior efficacy compared to standard aspirin, achieving up to 90% reduction in tumor growth in both human and mouse models, with minimal gastrointestinal side effects. Aspirin-PC is particularly effective when combined with VEGF inhibitors like Bevacizumab.¹⁷⁰ Moreover, aspirin inhibits the proliferation of COX-1 positive ovarian cancer cells by reducing EGF-induced signaling pathways such as Akt and Erk, suggesting a COX-1 dependent mechanism.¹⁷¹ The combination of aspirin with the HDAC inhibitor romidepsin (FK228) enhances its growth-inhibitory effects, upregulating p21 and delaying its degradation due to proteasome inhibition. This synergistic effect is observed in COX-1 positive ovarian cancer cells, highlighting aspirin's potential role in targeted therapies for specific ovarian cancer subtypes.¹⁷² Furthermore, aspirin reduces the invasive capacity of ovarian cancer cells by counteracting platelet-cancer cell interactions, suggesting its potential in reducing metastasis.¹⁷³

Aspirin and Pancreatic Cancer

Aspirin has garnered increasing attention as a promising therapeutic agent in the treatment and prevention of pancreatic cancer, with recent studies highlighting its multifaceted mechanisms. One of the key findings is that aspirin enhances the anti-tumor effects of gemcitabine by modulating N-glycosylation, specifically through dynamic changes in sialylation and high-mannose glycoforms on ECM-related proteins. This modulation can overcome chemoresistance, offering a promising avenue for improving pancreatic cancer therapies.¹⁷⁴ In KPC mice, aspirin has shown significant efficacy, reducing pancreatic ductal adenocarcinoma (PDAC) incidence by 15.6%, metastasis by 40%-56%, and PanIN lesions by 43.8%, while promoting tumor necrosis by up to 100%, underscoring its potential as an anti-PDAC agent.¹⁷⁵ Moreover, MDC-22, a phospho-aspirin derivative, has demonstrated strong therapeutic effects by inhibiting EGFR activation and downstream signaling pathways, such as ERK/FAK, and enhancing the efficacy of irinotecan, resulting in reduced tumor growth and extended survival in preclinical models.¹⁷⁶

Aspirin's action extends beyond chemotherapy enhancement; it also targets key pathways involved in inflammation and tumor progression. In combination with celecoxib, aspirin inhibits mammalian neuraminidase-1 (Neu-1) activity, blocking EGFR phosphorylation and inducing apoptosis in pancreatic cancer cells. This highlights its potential as a repurposed anti-cancer agent targeting glycosylation and EGFR-related pathways.¹⁷⁷ Additionally, the combination of aspirin with oseltamivir phosphate (OP) and gemcitabine enhances the therapeutic outcomes by reducing cell viability,

migration, and clonogenic potential, while also sensitizing cells to gemcitabine-induced apoptosis, thus overcoming chemoresistance.¹⁷⁸

Further studies show that aspirin plays a chemopreventive role in pancreatic cancer by delaying progression of precursor lesions (mPanINs) in genetically engineered mouse models. In one study, only 17.6% of mice treated with aspirin developed invasive pancreatic cancer, compared to 60% in untreated controls. Molecular analysis revealed significant downregulation of key genes, such as VEGF and RelA, which are crucial for cancer progression.¹⁷⁹ Additionally, aspirin has been found to inhibit platelet-induced upregulation of the oncogene c-MYC, effectively interrupting the pro-tumorigenic signaling in SW480 and PANC-1 cell lines.¹⁸⁰ As part of its multi-modal action, aspirin also suppresses NF-κB activity and reduces COX-2 expression, contributing to its tumor-suppressive effects. In preclinical models, aspirin-treated mice exhibited a significantly lower tumor incidence compared to untreated controls, with the most pronounced effects when aspirin was administered before or during tumor cell injection.¹⁸¹ Furthermore, aspirin's ability to inhibit Neu-1 activity and block the desialylation of α-2,3-sialic acid in EGF-stimulated pancreatic cancer cells correlates with reduced EGFR phosphorylation and the induction of apoptosis, reinforcing its anticancer potential through glycosylation modulation.¹⁷⁷

Aspirin's efficacy is further demonstrated in combination with gemcitabine in genetically engineered mouse models, where it significantly reduced the number of Foxp3⁺ regulatory T cells, suggesting an immunomodulatory effect that could potentiate the therapeutic outcomes of gemcitabine.¹⁸² Additionally, aspirin improves the efficacy of gemcitabine by inhibiting the accumulation of myeloid-derived suppressor cells (MDSCs) and M2-polarized tumor-associated macrophages, both of which contribute to immune evasion and chemoresistance. By addressing these mechanisms, aspirin improves gemcitabine's therapeutic outcomes.¹⁸³ Moreover, aspirin has been shown to counteract gemcitabine resistance by inducing G1 phase cell cycle arrest and enhancing the pro-apoptotic effects of gemcitabine in PANC-1 cells, primarily through the inhibition of GSK-3β, which suppresses downstream targets such as cyclin D1 and Bcl-2.¹⁸⁴ In combination therapy with gemcitabine, aspirin significantly increased apoptosis, evidenced by alterations in apoptosis-regulating proteins (Bax, Bcl-2), and reversed epithelial-mesenchymal transition (EMT), which contributes to its efficacy in conjunction with chemotherapy.¹⁸⁵ Additionally, aspirin inhibits PANC-1 cell proliferation through the PI3K/Akt/mTOR signaling pathway, further potentiating the anti-cancer effects when combined with gemcitabine.¹⁸⁶

However, it is important to note that combinations of aspirin with other agents, such as atorvastatin (Lipitor), may reduce its therapeutic benefits by promoting the expansion of M2 macrophages, emphasizing the need for careful selection of drug combinations in treatment strategies.¹⁸⁷ Thus, while aspirin offers significant promise in pancreatic cancer therapy, its optimal use may depend on precise drug pairing and dosing strategies.

Aspirin and Liver Cancer

Liver cancer, particularly hepatocellular carcinoma (HCC), continues to pose a significant global health challenge due to high mortality rates and limited treatment options. Recent research highlights aspirin's potential as a therapeutic agent against HCC through¹⁸⁸ its multifaceted mechanisms, targeting tumor growth, metabolic pathways, immune evasion, and drug resistance. One of the critical pathways influenced by aspirin involves platelet inhibition, which plays a key role in HCC progression. Platelets promote tumor growth, invasion, epithelial-mesenchymal transition (EMT), and an inflammatory microenvironment via the MAPK/AKT/STAT3 signaling axis. Aspirin effectively suppresses these processes in vitro and in vivo by inhibiting platelet activation and aggregation, demonstrating the therapeutic promise of antiplatelet therapy in managing HCC.¹⁸⁹ Aspirin exerts significant effects on metabolic pathways essential for HCC progression. It inhibits glycolysis by targeting PGAM1 succinylation through the NF-κB p65/HAT1/PGAM1 axis, reducing glucose consumption, enzymatic activity, and tumor growth.¹⁹⁰ Additionally, aspirin suppresses lysine 2-hydroxyisobutyrylation (Khib) on enolase 1 (ENO1), further decreasing glycolysis and lactate production.¹⁹¹ Aspirin also inhibits lipid metabolism by downregulating the NF-κB-ACSL1 axis, leading to reduced lipogenesis and decreased triglyceride and cholesterol levels in HCC cells.¹⁹² Moreover, aspirin targets glucose transporters, notably GLUT1, reducing glucose uptake and reactive oxygen species in HCC cells. High GLUT1 expression in HCC tissues correlates with poor prognosis, highlighting aspirin's potential to improve outcomes by targeting metabolic vulnerabilities.¹⁹³

Aspirin has shown significant immunomodulatory effects in HCC, particularly by suppressing immune evasion mechanisms. It decreases PD-L1 expression, thereby enhancing the immune response against HCC cells.¹⁹⁴ Furthermore, aspirin induces ferroptosis, a form of cell death, by inhibiting NF-κB p65-mediated transcription of SLC7A11, an inhibitor of ferroptosis. Combining aspirin with ferroptosis inducers like erastin enhances this effect, offering a promising therapeutic strategy for HCC treatment.¹⁹⁵ Beyond metabolic and immune modulation, aspirin reduces cancer stemness and regulates epigenetic changes in HCC. It suppresses ICAM3 expression and modulates histone methylation via KDM6A/B inhibition, operating through COX-independent pathways.¹⁰¹ Additionally, aspirin downregulates TCF4 and LEF1 while inhibiting the nuclear translocation of β-catenin, disrupting the Wnt/β-catenin pathway. This inhibition reduces HCC proliferation and induces apoptosis.¹⁹⁶ Aspirin also enhances autophagy by increasing the LC3II/LC3I ratio and reducing p62 expression. This effect, mediated by Beclin-1 and AMPK activation, disrupts the mTOR pathway, further supporting its therapeutic role.¹⁹⁷

In combination therapies, aspirin demonstrates significant potential by enhancing the efficacy of other treatments. Aspirin combined with vitamin C shows superior anti-HCC activity compared to doxorubicin, improving liver histopathology and reducing toxicity.¹⁹⁸ When paired with sorafenib, aspirin minimizes its pro-metastatic effects by upregulating HTATIP2 and sensitizing HCC cells via glycolysis inhibition and apoptosis induction.^{199,200} Aspirin also synergizes with metformin, inducing apoptosis and cell cycle arrest in HCC cells through the downregulation of AMPK and mTOR pathways.²⁰¹ Furthermore, aspirin enhances the anticancer effects of Navitoclax by suppressing Mcl-1 expression and triggering mitochondrial apoptosis.²⁰² It also improves the therapeutic effects of interferon-α by promoting STAT1 phosphorylation via JAK1 activation.²⁰³ Aspirin in combination with valproic acid significantly reduces tumor volume in murine models,²⁰⁴ and it sensitizes HCC side population cells to doxorubicin by regulating the miR-491/ABCG2 pathway, improving drug sensitivity.²⁰⁵ Aspirin induces apoptosis in HCC through both intrinsic and extrinsic pathways by altering the Bax/Bcl-2 ratio and activating caspases. In vivo studies have shown that oral administration of aspirin significantly reduces tumor growth in BALB/c nude mice.²⁰⁶ Moreover, aspirin targets the tumor microenvironment by inhibiting P4HA2, leading to decreased collagen deposition and improved prognosis in HCC patients.²⁰⁷ It also influences extracellular matrix remodeling, addressing concerns related to tumor progression and resistance. In summary, aspirin demonstrates broad and promising efficacy in the treatment of hepatocellular carcinoma by targeting key metabolic, immune, and signaling pathways. Its versatility extends to combination therapies with existing drugs, offering enhanced safety and efficacy. Ongoing research into aspirin's molecular mechanisms and clinical applications is expected to further solidify its role as a valuable adjunct in liver cancer management.

Aspirin and Other Cancers

Aspirin has demonstrated significant potential in addressing various cancers beyond those discussed earlier. In breast cancer, it shows promise by targeting estrogen receptor alpha (ER α), binding to its ligand-binding domain (LBD) with stability comparable to selective estrogen receptor modulators (SERMs). This mechanism reduces ER α expression in MCF-7 cells, making aspirin a candidate for treating tamoxifen-resistant breast cancers.²⁰⁸ Low-dose aspirin enhances radiotherapy in breast cancer by inhibiting exosome release, boosting natural killer cell proliferation, and promoting cancer cell apoptosis, thus increasing radiotherapy sensitivity.²⁰⁹ Additionally, aspirin downregulates the NF-κB pathway, inhibiting TNF-α-mediated cell survival, although it does not sensitize breast cancer cells to necroptosis when combined with chemotherapy.²¹⁰ Aspirin selectively suppresses PIK3CA-mutant breast cancer cells by activating AMPK, inhibiting mTORC1, and inducing autophagy, effects that are independent of COX-2 and NF-κB. This action is further enhanced when combined with PI3K inhibitors, making it a promising combination therapy.²¹¹ Moreover, aspirin addresses breast cancer chemoresistance by disrupting the NFκB-IL6 loop, preventing recurrence, and improving cancer stem cell sensitivity to chemotherapy.²¹² It also promotes Bcl-2 nuclear translocation and phosphorylation, enhancing apoptosis in estrogen receptor-positive breast cancers.¹⁸³ Aspirin further reduces breast cancer metastasis by sensitizing cancer cells to anoikis, thereby decreasing circulating tumor cells and lung metastasis through inhibition of the thromboxane A2 (TXA2) pathway.²¹³

In prostate cancer, aspirin reduces the risk of TMPRSS2-ERG (T2E) fusion-positive prostate cancer by 37%, while having negligible effects on T2E-negative cases.²¹⁴ It inhibits prostate cancer cell proliferation by downregulating the

androgen receptor (AR) and prostate-specific antigen via EP3 receptor signaling, and it restricts cancer cell invasion by reducing MMP-9 activity, downregulating uPA expression, and upregulating TIMP-1 to limit extracellular matrix degradation.^{215,216} In gastrointestinal cancers, aspirin promotes mucosal healing and suppresses tumor growth by upregulating TFF2 transcription, mediated by protein kinase C, further establishing its role in chemoprevention.²¹⁷

Aspirin also demonstrates chemopreventive effects in cervical cancer. It reduces tumor growth and delays tumor onset in HPV16-transformed cells, while increasing survival in tumor-bearing mice, making it a promising agent for cervical cancer management.²¹⁸ In glioblastoma, aspirin targets the SHH/GLI1 pathway to prevent GLI1 nuclear translocation, reprogram EMT, and enhance chemosensitivity to temozolomide (TMZ) by impairing DNA repair. It also boosts the cytotoxic effects of nitric oxide (NO) donors, inhibits the β -catenin/TCF pathway, and downregulates IL-6-dependent STAT3 signaling, reducing the expression of survival-related genes such as Cyclin D1, XIAP, and Bcl-2. These mechanisms highlight aspirin's potential to overcome chemoresistance and induce apoptosis in glioblastoma.^{91,219–221}

Aspirin has shown efficacy in melanoma when combined with fisetin, significantly reducing cell viability, inducing apoptosis, and disrupting tubulin filaments in A375 melanoma cells.¹³¹ In uterine leiomyoma, aspirin induces G0/G1 cell cycle arrest by disrupting the K-RAS-p110 α interaction and altering cell cycle regulators such as cyclin D1 and CDK2, while modulating the PI3K/Akt/caspase signaling pathway.¹⁶⁵ It also demonstrates pro-apoptotic effects in leukemia by disrupting the Mcl-1/Noxa balance independently of the NF- κ B and MAPK pathways.²²² In osteosarcoma, aspirin sensitizes cells to cisplatin, reduces cell migration and invasion, and decreases lung metastasis by suppressing the NF- κ B pathway. It also induces dose-dependent apoptosis and necrosis in osteoblast models, highlighting its potential in bone cancers.^{223,224} In gingivobuccal squamous cell carcinoma (GB-SCC), aspirin inhibits the PLA2G6 enzyme, while in oral squamous cell carcinoma (OSCC), it blocks proliferation, migration, and invasion through the PI3K-Akt and focal adhesion pathways, demonstrating its utility in head and neck cancers.^{225,226} In summary, aspirin demonstrates broad anticancer efficacy across a range of malignancies, targeting key molecular pathways such as NF- κ B, STAT3, Wnt/ β -catenin, and SHH/GLI1. Its ability to enhance the efficacy of existing therapies, reduce metastasis, and overcome chemoresistance underscores its potential as a valuable therapeutic and chemopreventive agent. Future research into optimizing aspirin formulations and exploring its mechanisms further will continue to expand its role in oncology. An Overview of the efficacy of aspirin in different cancer is depicted in Table 3.

Aspirin and Clinical Outcome

The clinical utility of aspirin against various human cancers has been extensively evaluated through in vivo studies, clinical trials, and meta-analyses. Aspirin demonstrates significant potential in cancer prevention, recurrence reduction, and survival improvement across multiple malignancies. A Phase III trial evaluated aspirin (200 mg daily) as adjuvant therapy for colorectal cancer (CRC) in 1550 patients across 10 Asia-Pacific countries, reporting 5-year disease-free survival (DFS) rates of 77% (aspirin) and 75% (placebo), with no significant DFS or overall survival (OS) benefits. However, a moderate benefit cannot be excluded, and ongoing biomarker analyses may identify subpopulations likely to benefit from aspirin. Aspirin was well tolerated, supporting its potential as a low-cost option for CRC prevention pending further studies.²²⁷ A meta-analysis of 11 RCTs (92,550 participants) found that high-dose aspirin (500–1200 mg/day) significantly reduced CRC incidence (OR 0.69, 95% CI 0.50–0.96), while mid- and low-dose aspirin showed no significant effect. Although promising, these findings underscore the need for additional research to optimize aspirin dosing for cancer prevention.²²⁸

Postoperative adjuvant aspirin significantly extended the time to recurrence of portal vein tumor thrombus (PVTT) compared to surgery alone in patients with HBV-related hepatocellular carcinoma (HCC) and PVTT. Elevated COX-1 or COX-2 expression correlated with better prognosis in the aspirin group, highlighting its potential to improve outcomes for this patient population.²²⁹ Persistently elevated thromboxane biosynthesis was observed post-radical cancer therapy, particularly in colorectal and gastro-esophageal cancer patients, correlating with higher BMI and inflammatory markers. Aspirin at 100 mg daily significantly reduced thromboxane levels by 77–82%, with no additional benefit at 300 mg. These findings highlight thromboxane as a potential biomarker for malignancy and a target for aspirin therapy to prevent or delay metastases.²³⁰ In BRAF-mutant CRC, aspirin reduced metastatic incidence without affecting primary tumor development, significantly lowering lesion size ($P = 0.0042$) and metastasis risk (RR 0.69, $P = 0.0134$). Key metastasis-driving pathways, including NOTCH, FGFR, and PI3K signaling, were downregulated in aspirin-treated mice, suggesting a preventive role in molecular changes driving metastasis.²³¹ Additionally, regular aspirin use in chronic liver disease

Table 3 Overview of the efficacy of Aspirin in Different Cancer

Cancer Type	Cell Line Used/ Animal Model	Model	Aspirin Concentration Used	Target Pathways/ Key Proteins Involved	Therapeutic Outcome/ Implications
Colon Cancer	SW620, LoVo, RKO and DLD-1 cells	In vivo In vitro	2mM 10mg/kg	Bcl-2, PARP, Bax, PI3K/AKT, NF- κ B/COX-2 Microbiota modulation, Lysinibacillus sphaericus, Bifidobacterium, Lactobacillus	Enhanced cisplatin efficacy, apoptosis induction, reduced proliferation, migration, and invasion Reduced tumorigenesis linked to microbiota changes, impact on aspirin efficacy
Colorectal Cancer	APCmin/+ mice	In vivo	1 mM	COX-1, COX-2, prostaglandin E2, TXB2	Potent inhibition of thromboxane B2 production, no pro-inflammatory eicosanoid generation
Colorectal Cancer	HCA7 cells	In vitro	100 mg/kg	c-MYC, calreticulin, HSP70, CD8 + T cells, PD-1, CTLA-4	Enhanced antitumor responses with immune checkpoint inhibitors, immunogenic cell death
Colorectal Cancer	CT26, SW480, HT29,	In vitro, In vivo	200 ppm	Fusobacterium nucleatum, gut microbiota	Reduction in F. nucleatum-potentiated tumorigenesis, chemoprevention via microbiome modulation
Colorectal Cancer	Fusobacterium nucleatum, ApcMin/+ mice	In vivo	2.5–5 mM	Sp1, Sp3, Sp4, bcl-2, VEGF, Wnt signaling	Apoptosis induction, inhibition of tumor growth, immune response enhancement
Colorectal Cancer	RKO, SW480, HT-29 and HCT-116	In vitro	0.5–10 mM	EMT, Wnt signaling, ZEB1, Snail family, TGF- β 1	Inhibition of epithelial-mesenchymal transition, reduced cell viability and migration
Colorectal Cancer	SW480 cells	In vitro	100 –2500 μ M)	Glucose-6-phosphate dehydrogenase, transketolase	Inhibition of glycolysis and ribonucleotide biosynthesis, modulation of key cellular proteins
Melanoma	B16-F0 mouse melanoma cells	In vivo	Tumor growth inhibited by 50% at 150 mg/kg ASA for 13 days, 100 μ M for cells derived from mouse	Reactive oxygen species (ROS), GSH depletion	Supports epidemiological evidence linking aspirin with reduced melanoma risk in humans
Melanoma	B16 melanoma cells, PDX lines MTG2 (HCIMel002) and MTG4 (HCIMel004)	In vitro	Significant suppression of cell proliferation and motility at 1 mmol/L and 20 μ mol/L	Prostaglandin E2 (PGE2), AMPK	Preclinical models showed ASA reduced tumor growth in sensitive melanoma tumors, supporting its potential as a chemopreventive agent
Melanoma	B16 melanoma cells	In vitro	0.5–5 mM	JNK, p38 mitogen-activated protein kinases	Aspirin suppresses proliferation in B16 cells; combination with BCNU induces synergistic cell death
Melanoma	YUMM 1.7	In vivo	Three concentrations in drinking water for mice: Low (LO) – 300 μ g/mL Medium (MED) – 600 μ g/mL High (HI) – 1000 μ g/mL	PD-1, CD8+ T-cells, monocytes	ASA increases PD-1+ CD8+ T-cells in tumor microenvironment; potential as adjunct to anti-PD-1 therapy
Melanoma	G361, SK-MEL-30, DM-738, SK-MEL-2, and SK-MEL-28	In vitro	1–6mM	MITF-M, Wnt signaling, β -catenin	Combination of aspirin and indole-3-carbinol reduces MITF-M expression and inhibits cell proliferation

(Continued)

Table 3 (Continued).

Cancer Type	Cell Line Used/ Animal Model	Model	Aspirin Concentration Used	Target Pathways/ Key Proteins Involved	Therapeutic Outcome/ Implications
Melanoma	B16F0 melanoma cells	In vivo, In vitro	1 mM aspirin	Matrix metalloproteinase-2 (MMP-2), PGF2 α	Aspirin inhibits MMP-2 activity and invasion of B16F0 melanoma cells, reducing colorectal metastasis
Melanoma	B16 melanoma cells, SK-MEL	In vitro, In vivo	0.1 to 10 mM	Caspase 3/7, PGF2 α , SOX-2	ASA induces apoptosis in melanoma cells; inhibits tumor growth independently of PAF-R
Melanoma	A375 melanoma cells	In vitro	ASA 2.5 mM and FIS 20 μ M	–	ASA and fisetin combination enhances cytotoxicity, inhibiting cell viability and angiogenesis
Melanoma	A2058	In vitro	\geq 2.5 mM	Mitochondrial Ca $^{2+}$, ROS, caspase-dependent apoptosis	Aspirin sensitizes melanoma cells to TRAIL-induced apoptosis, suggesting potential in combination therapies
Melanoma	Human patients	In vivo	–	Prostaglandin E2 (PGE2), AMPK	High-dose ASA combined with pembrolizumab and ipilimumab showed 62.9% response rate; significant survival benefits for patients continuing ASA treatment
Lung Cancer	A549, H1299	In vitro	2.5–5mM	miR-98, WNT1	Aspirin suppresses lung cancer cell viability and colony formation by modulating the miR-98/WNT1 axis
Lung Cancer	Lewis lung carcinoma (LLC) cells	In vivo	100 mg/kg	COX inhibitors	Aspirin inhibits metastasis to lymph nodes without affecting primary tumor growth, significantly reducing mortality in mice
Lung Cancer	A549 and H1299	In vitro	2.5 mM and 5.0 mM	PD-L1, TAZ transcriptional coactivator	Aspirin inhibits lung cancer cell proliferation by downregulating PD-L1 expression through TAZ, contributing to tumor growth suppression
Lung Cancer	CL1-0, A549	In vitro	2 mM	Caspase-3, Bcl-2, dihydrofolate reductase (DHFR)	Aspirin antagonizes methotrexate's cytotoxicity, suggesting potential adverse effects when used concurrently in lung cancer therapy
Non-Small Cell Lung Cancer (NSCLC)	A549	In vitro	2.5mM, 10mM	miR-135b, miR-210, G2/M cell cycle arrest	Aspirin induces G2/M arrest and reduces hypoxia-induced stemness, potentially enhancing therapeutic outcomes in NSCLC
Lung Cancer	CL1-0 and A549 cells	In vitro	2mM	Caspase-3, PARP, p27, PI3K/Akt	Troglitazone and aspirin show synergistic effects in inducing G1 arrest and apoptosis, downregulating key cell cycle proteins
Non-Small Cell Lung Cancer (NSCLC)	A549 and H1299	In vivo	5Mm and 8mM	Caspase-9, Caspase-3, ERK-MAPK, MMP-2, MMP-9	Aspirin and celecoxib synergistically induce cell cycle arrest and inhibit NSCLC cell migration and invasion through MMP activity inhibition

Lung Cancer	H460 cisplatin-sensitive (H460S) and H460 cisplatin-resistant (H460R)	In vitro, In vivo	16 µM	mTOR/Akt axis, stemness factors	Aspirin enhances cisplatin sensitivity in resistant lung cancer cells, suggesting it as a promising adjunct therapy to overcome cisplatin resistance
Non-Small Cell Lung Cancer (NSCLC)	NSCLC cell lines SK-MES-1, SK-LU-1 and COLO 699N	In vitro	1 µM, 100 µM, and 1 mM	NFkB, bcl-2, bcl-XL, surviving	Aspirin activates NFkB-dependent anti-apoptotic pathways, which may limit its efficacy in NSCLC chemoprevention by promoting apoptosis resistance
Non-Small Cell Lung Cancer (NSCLC)	A549 and H1299	In vitro	2 mM	β-catenin/STAT3 signaling	Aspirin and decitabine combination therapy inhibits tumor growth and migration by reducing β-catenin and STAT3 expression, showing promise for NSCLC treatment
Lung Cancer	PC-9, A549	In vitro	1–16mM	MAPK signaling (ERK, p38, JNK pathways)	Low-dose aspirin promotes lung cancer cell proliferation through activation of MAPK signaling, indicating that low-dose aspirin may have a growth-promoting effect in lung cancer
Non-Small Cell Lung Cancer (NSCLC)	NCI-H460, NCI-H1975 (H1975) and A549	In vitro	0.5mM	p53, EGFR, JNK, AKT, mTOR	Triple therapy with aspirin, afatinib, and vinorelbine shows synergistic inhibition of tumor growth, suggesting a potential new combination therapy for wild-type p53 NSCLC
Non-Small Cell Lung Cancer (NSCLC)	K-ras-expressing NSCLC cells	In vitro	Not reported	E-cadherin, Slug, p65NFkB	Aspirin downregulates Slug and upregulates E-cadherin, reducing the metastatic potential of K-ras-expressing NSCLC cells
Non-Small Cell Lung Cancer (NSCLC)	A549 cells	In vitro, in vivo	0.1–160 mM	VEGF	Aspirin reduces tumor growth and angiogenesis in NSCLC models by inhibiting VEGF, supporting its role in combination chemotherapy
Lung Cancer	A549 cells, ASA-UPFUC derivative	In vitro	IC50 = 49.09 µg/mL (50.20% lower than UPFUC)	Mitochondrial apoptotic pathway	Aspirin derivative ASA-UPFUC shows enhanced antitumor activity in A549 lung cancer cells, suggesting its potential as a dietary additive for chemoprevention
Non-Small Cell Lung Cancer (NSCLC)	A549,H460,H1299	In vitro	2.5 mM	mTOR, Akt, Snail, β-catenin, Integrin/Fak pathway	Aspirin pre-treatment enhances the efficacy of cisplatin in repressing cancer stem cell migration by inhibiting mTOR gene transcription, showing potential in metastatic NSCLC treatment
Non-Small Cell Lung Cancer (NSCLC)	NCI-H1299 and A549	In vitro, in vivo	2–10mM	E-cadherin, p38 pathways	Combination of aspirin and erlotinib enhances anti-proliferative and anti-metastatic effects, with potential for improving metastatic NSCLC treatment

(Continued)

Table 3 (Continued).

Cancer Type	Cell Line Used/ Animal Model	Model	Aspirin Concentration Used	Target Pathways/ Key Proteins Involved	Therapeutic Outcome/ Implications
Ovarian Cancer	HeyA8, SKOV3ip1, and A2780	In vitro	0.025–1mM	VEGF pathway	Aspirin-PC exhibited superior efficacy in reducing tumor growth and angiogenesis without gastrointestinal toxicity. Combination with VEGF inhibitors shows promise.
Epithelial Ovarian Cancer (EOC)	EOC cell lines (SK-OV-3), In vivo studies	In vitro/ In vivo	Enhanced sensitivity to cisplatin (CDDP)	p53 acetylation, activation of CDKN1A, BAX, FOXFI, PUMA	Aspirin enhanced the sensitivity of EOC cells to CDDP, leading to significant tumor growth inhibition
Ovarian Cancer	A2780, Caov-3 and SK-OV-3	In vitro	25 µM - 1000 µM	Epithelial-to-mesenchymal transition (EMT), platelet-cancer interactions	Aspirin counteracted the EMT phenotype promoted by platelets, reducing invasion and metastatic potential
COX-I Positive Ovarian Cancer	OVCAR-3, SKOV-3, TOV-21G and CaOV-3	In vitro	0.25–1 mmol/L	COX-I dependent, decreased Akt and Erk phosphorylation	Aspirin inhibited cell proliferation in COX-I positive ovarian cancer cells by targeting Akt and Erk pathways. No effect on COX-I negative cells.
COX-I Positive Ovarian Cancer	OVCAR-3 (COX-I positive) and SKOV-3 (COX-I negative)	In vitro	0.25mM–1mM	Upregulation of p21, inhibition of proteasome activity	Aspirin enhanced the efficacy of the HDAC inhibitor FK228 in COX-I positive cells, suggesting targeted therapy potential
Pancreatic Cancer	PANC-1, Capan-1	In vitro	0.5–4mM	GSK-3β, cyclin D1, Bcl-2	Aspirin enhances gemcitabine efficacy by inducing apoptosis and suppressing pathways associated with chemoresistance.
Pancreatic Cancer	Mice (genetically engineered model) Conditional LsL-Trp53R172H, 19 LsL-KrasG12D and Pdx1-Cre4	In vivo	20 mg/kg	VEGF, RelA	Aspirin significantly reduced the incidence of invasive pancreatic cancer in treated mice compared to controls.
Pancreatic Cancer	PANC-1	In vivo, In vitro	0.5–10mM	NF-κB, Cox-2	Aspirin demonstrated preventive effects against tumorigenesis when administered before or during tumor cell injection.
Pancreatic Cancer	SW1990 and BxPC-3 cell lines	In vitro	2 mmol	PI3K/AKT/mTOR, EMT	Aspirin significantly boosted the efficacy of gemcitabine, leading to reduced proliferation and altered apoptosis-regulating proteins.
Pancreatic Cancer	PANC-1 (human pancreatic carcinoma, epithelial-like, ATCC CRL-1469) and MiaPaCa-2	In vitro	0.1 mM to 12.8 mM	Neu-1, EGFR	Aspirin inhibition of Neu-1 activity correlates with apoptosis induction and suppression of EGFR phosphorylation, linking it to glycosylation processes involved in tumorigenesis.
Pancreatic Cancer	Mice (genetically engineered model) Conditional LsL-Trp53 ^{R172H} , LsL-Kras ^{G12D} , and Pdx1-Cre	In vivo	40 mg/kg	Foxp3+ regulatory T cells	Aspirin showed potential as an adjuvant to gemcitabine, enhancing median survival and suggesting an immunomodulatory effect.

Liver Cancer	HepG2 and HCCLM	In vitro	2 and 4 mM	Wnt/β-catenin, TCF4, LEFI	Aspirin inhibits HepG2 proliferation and promotes apoptosis through the Wnt/β-catenin signaling pathway.
Liver Cancer	HepG2 and HCCLM	In vitro, in vivo	In vitro studies was 0.1–10 mmol/L	HTATIP2, COX-2	Aspirin enhances anti-invasion and anti-metastatic properties, minimizing the pro-metastatic effects of sorafenib.
Liver Cancer	HCC cell lines HepG2 and BEL-7402	In vitro	2.5Mm-10mM	Mcl-1, cytochrome c, caspases	Aspirin acts as an adjuvant to Navitoclax, improving anticancer effects and overcoming resistance due to Mcl-1.
Liver Cancer	HCC-LM3, SMMC-7721, Hep3B, Bel-7402 and Huh7	In vitro	5 mM	Glycolytic pathway, PFKFB3	Aspirin overcomes drug resistance and induces apoptosis, suggesting a promising treatment approach for HCC.
Liver Cancer	HCC Bel-7402 and MHCC97L	In vitro, In vivo	1 mM	JAK1, Bax, GIP3	Aspirin enhances antitumor effects of interferon-α, improving its therapeutic potential in HCC treatment.
Liver Cancer	Huh7, HepG2, SMMC-7721, Hep3B and H22	In vitro	2–12μM	Survivin, Bcl-2/Bax, Cyclin D1	Combination with valproic acid enhances apoptotic activity, suggesting a potential therapeutic strategy.
Liver Cancer	HepG2,BALB/c nude mice	In vivo, In vitro	5–15μM	Caspases, Bax/Bcl-2 ratio	Aspirin serves as a promising anticancer agent against liver cancer through apoptosis induction.
Liver Cancer	HepG2 and Huh-7	In vivo, In vitro	2–4 mM	P4HA2, NF-κB	Aspirin regulates P4HA2 expression, enhancing therapeutic potential and correlating with better prognosis in HCC.
Liver Cancer	HepG2 and Huh7 cells	In vitro, In vivo	4mM	SLC7A11, NF-κB p65	Aspirin enhances ferroptotic effects, suggesting potential as a therapeutic strategy in HCC treatment.
Liver Cancer	Hep3B, HepG2, SMMC-7721 cells	In vitro	5mM	Beclin-1, mTOR-S6K1/4E-BP1	Aspirin's effects on autophagy elucidate mechanisms of chemoprotective effects against HCC development.
Liver Cancer	HepG2,H7402	In vitro, In vivo	2Mm-4mM	GLUT1, NF-κB	Aspirin suppresses abnormal lipid metabolism, indicating therapeutic potential for targeting GLUT1 in HCC.
Liver Cancer	MHCC-97L	In vitro	1.25–5 μmol/mL	miR-491, ABCG2	Aspirin modulates drug sensitivity in HCC cells, indicating a critical role of the miR-491/ABCG2 pathway.
Liver Cancer	HepG2 and Huh7 cells	In vitro	2.5–5mM	ACSL1, NF-κB	Aspirin inhibits lipid metabolism, suggesting a potential therapeutic role in controlling HCC.
Prostate Cancer	TMPRSS2-ERG positive/negative PCa (preclinical models)	In vivo	700 and 1400 ppm	TMPRSS2-ERG fusion, inflammation-related pathways	Specificity in reducing high-grade adenocarcinoma in fusion-positive PCa
Prostate Cancer	DU145, LNCaP, and 22Rv1	In vitro	0.1–5mM	Androgen receptor (AR) downregulation, EP3 receptor signaling	Inhibits proliferation and PSA levels, potential therapeutic target in androgen-dependent PCa

(Continued)

Table 3 (Continued).

Cancer Type	Cell Line Used/ Animal Model	Model	Aspirin Concentration Used	Target Pathways/ Key Proteins Involved	Therapeutic Outcome/ Implications
Prostate Cancer	DU145, LNCaP and PC-3	In vitro	5 mmol/l	NF-κB inhibition, MMP-9 downregulation, TIMP-1 upregulation	Inhibits cancer invasion and metastasis, chemopreventive potential
Gastrointestinal Cancer	MKN45 and Kat0111	In vitro	15 and 25 mM	TFF2 transcription, PKC activation	Chemoprevention via mucosal healing and TFF2 upregulation
Uterine Leiomyoma	GM10964	In vitro	0.2–10 mmol/l	K-Ras-pI10α interaction disruption, PI3K/Akt pathway	Induces G0/G1 arrest and apoptosis, potential novel treatment for uterine leiomyoma
Leukemia	Human leukemic T cell lymphoblast Jurkat (clone E6-1), human caucasian Burkitt's lymphoma Ramos and human lymphoblastoid TK6 cell lines	In vitro	0–10 mM	Mcl-1 downregulation, Noxa upregulation	Induces apoptosis via BIM, NOXA, PUMA
Glioma	U87 and T98G	In vitro	2–10mM	SHH/GLII pathway inhibition, EMT reprogramming	Enhances TMZ sensitivity, inhibits DNA repair
Glioblastoma	U87 and A172 glioma cells	In vitro	0.5–20mM	β-catenin/TCF inhibition, c-myc suppression	Inhibits proliferation, invasion, induces apoptosis
Glioblastoma	A172 glioma cells	In vitro	5–8mM	IL-6/STAT3 pathway inhibition, STAT3 phosphorylation	Reduces cell survival via downregulation of Cyclin D1, XIAP, and Bcl-2
Breast Cancer	MCF10A, SUM159-PT, MCF7, MDA-MB-468, and MDA-MB-231.	In vitro, in vivo	1–5 mmol/L	AMPK activation, mTORCI inhibition, autophagy	Selectively suppresses mutant cell growth, potential for combination therapy
Breast Cancer	MCF-7, T47D, ZR-75-1, MDA-MB-361	In vitro	2.5mM	NFκB-IL6 loop disruption	Prevents chemoresistance, improves CSC sensitivity to chemotherapy
Breast Cancer	MCF-7 and MDA-MB231	In vitro	1–100μmol	Bcl-2/FKBP38 complex formation, nuclear translocation	Enhances apoptosis in Bcl-2-positive cancers
Breast Cancer	A549 and H1299	In vivo	2mM	TXA2 pathway inhibition, Akt suppression	Reduces anoikis resistance, lung metastasis
Osteosarcoma	U2OS, MG63, ZOS, U2OS/MTX300, and HEK-293T	In vitro, in vivo	7.5 mmol/L	NF-κB pathway inhibition	Sensitizes cells to cisplatin, reduces metastasis
Gingivobuccal SCC	ITOC-03 and ITOC-04	In vitro, in vivo	2.5 and 5 mmol/L	PLA2G6 enzyme inhibition, COX and LOX components	Suppresses tumor growth, synthetic lethality in AAM pathway
Oral SCC	TCA8113 and CAL27	In vitro	2mM	PI3K-Akt pathway inhibition, NF-κB, STAT3 downregulation	Blocks proliferation, induces apoptosis

reduced HCC incidence by 54% (HR 0.46, $P < 0.001$) in general and by 28% (HR 0.72, $P < 0.001$) in patients with viral hepatitis, with no significant increase in major gastrointestinal bleeding risk (HR 1.00, $P = 0.90$). This meta-analysis highlights aspirin's potential as a chemopreventive agent for HCC.²³² Low-dose aspirin use has been linked to a reduced risk of ovarian cancer, particularly in nulliparous women (OR 0.80) and those without cardiovascular disease (OR 0.91). These findings highlight the need for further subgroup-specific analyses to optimize its preventive potential.²³³ Aspirin has also been inversely associated with head and neck cancer risk, with an overall odds ratio of 0.48. Subgroup analyses revealed similar protective effects for laryngeal cancer (OR 0.54). Longer aspirin use further supports these findings, showing inverse associations for oropharyngeal and laryngeal cancers.²³⁴

Aspirin and ibuprofen reduce the risk of advanced adenomas, recurrent adenomas, and CRC in older adults. Aspirin significantly lowers advanced recurrent adenoma risk (OR 0.56), while ibuprofen reduces incident adenoma (OR 0.76) and CRC risk (HR 0.81). These findings underscore their potential in colorectal neoplasia prevention.²³⁵ Aspirin therapy is significantly associated with a reduced risk of HCC in non-alcoholic fatty liver disease (NAFLD) patients, especially with long-term use (≥ 3 years). In a cohort study of over 88,000 patients, the 10-year cumulative incidence of HCC was markedly lower in aspirin users (0.25% vs 0.67%; $P < 0.001$), with high-risk individuals showing similar trends (3.59% vs 6.54%; $P < 0.001$).²³⁶ Prophylactic low-dose aspirin use is associated with reduced all-cause mortality in cancer patients. In a cohort study involving 1819 participants from NHANES data (2011–2018), aspirin users had a 35% lower risk of all-cause death (HR 0.647, 95% CI 0.489–0.857) compared to non-users, suggesting aspirin's potential role in improving overall survival among cancer patients.²³⁷ Post-diagnosis aspirin use significantly improved 10-year OS in CRC patients with wild-type PIK3CA and mutated-KRAS tumors (HR 0.38; $P = 0.02$). This underscores aspirin's potential as an effective adjuvant therapy for specific genetic profiles.²³⁸

Aspirin intake has also been shown to alter the gut microbiome in healthy adults, increasing taxa such as Akkermansia and Prevotella while decreasing Parabacteroides and Dorea. These changes are consistent with associations linking aspirin to reduced CRC risk, warranting further study in larger trials.²³⁹ Furthermore, a systematic review of 118 observational studies across 18 cancers found a 20% reduction in cancer-specific and all-cause mortality with aspirin use.²⁴⁰ A meta-analysis of 23 randomized trials demonstrated that low-dose aspirin reduced nonvascular mortality, including cancer deaths, with a relative risk of 0.77. Notably, these therapeutic effects were more evident after approximately four years of follow-up.²⁴¹ Aspirin use in chronic obstructive pulmonary disease (COPD) patients was associated with a 25% lower risk of lung carcinoma and a 26% decline in lung carcinoma-related mortality.²⁴² A meta-analysis of 42 studies involving over 99,000 participants found that regular aspirin use for more than three years significantly reduced the overall risk of breast cancer, particularly in postmenopausal women.²⁴³ Regular aspirin use was also associated with improved survival rates in bladder (HR 0.67) and breast cancer (HR 0.75).²⁴⁴

Long-term low-dose aspirin use was linked to a 36% reduction in gastric cancer risk (OR 0.64) in a meta-analysis of 21 studies.²⁴⁵ Aspirin administration was also found to reduce gastrointestinal cancer mortality, with benefits becoming more pronounced after five years of treatment (HR 0.46 for gastrointestinal cancers).²⁴⁶ Additionally, aspirin was comparable to enoxaparin in managing cancer-associated acute ischemic stroke (AIS). Aspirin's safety and efficacy, along with better patient compliance, suggest its potential as an alternative to anticoagulation in cancer-related AIS.²⁴⁷ Long-term aspirin use (≥ 5 years) at doses ≥ 300 mg/day significantly reduced CRC incidence. Notable effects emerged after a 10-year latency, highlighting aspirin's potential in long-term disease prevention.²⁴⁸ Additionally, aspirin significantly reduced CRC recurrence and mortality by 17% and 21%, respectively, and suppressed distant metastasis (HR 0.54).^{249,250} The ASPIRED trial further demonstrated aspirin's effect on reducing urinary PGE-M levels, a biomarker associated with CRC risk, by 15–28%.²⁵¹ Lastly, post-diagnostic aspirin use improved cancer-specific survival (HR 0.78) in CRC patients with PIK3CA mutations and PTGS2 expression.²⁵² Aspirin demonstrates significant potential in managing cancer and associated conditions. In cancer-associated acute ischemic stroke (AIS), aspirin was as effective as enoxaparin, with comparable outcomes for major bleeding and survival, and was better tolerated by patients.²⁵³ Daily aspirin use significantly reduced cancer mortality and inhibited adenocarcinoma progression, particularly in colorectal cancer, suggesting benefits beyond prevention.²⁵⁴ A systematic review highlighted aspirin's ability to lower risks of digestive tract cancers, including colorectal, esophageal (RR 0.67), gastric (RR 0.64), and pancreatic (RR 0.78) cancers.²⁵⁵ In ovarian cancer, frequent aspirin use (≥ 6 days/week) was linked to a 13% risk reduction, with consistent benefits observed across high-risk populations.^{256,257} In pancreatic cancer, the ESPAC-4 trial showed that aspirin significantly improved survival, with

median DFS and OS increasing to 17.9 and 42.4 months, respectively, compared to non-users.²⁵⁸ These findings underline aspirin's role as both a preventive and adjunctive therapy in improving outcomes for various malignancies. Aspirin demonstrates broad clinical benefits across malignancies, including colorectal, liver, ovarian, pancreatic, breast, and lung cancers. Its ability to reduce cancer incidence, prevent metastases, and improve survival supports its role as a preventive and therapeutic agent. Future research should focus on optimizing dosage, duration, and identifying responsive subgroups to maximize its clinical potential.

Application of Aspirin in Other Diseases

Aspirin, widely recognized for its analgesic, antipyretic, and anti-inflammatory properties, has demonstrated significant therapeutic potential beyond these primary uses. Recent advancements highlight aspirin's role in combating bacterial, viral, and fungal infections, as well as its application in neurological, cardiovascular, and metabolic diseases.

Antibacterial Effects of Aspirin

Aspirin (acetylsalicylic acid, ASA) exhibits significant antibacterial properties, primarily through its conversion to salicylic acid. It inhibits *Helicobacter pylori* growth in a dose-dependent manner, enhances antibiotic efficacy against amoxicillin, clarithromycin, and metronidazole, and suppresses resistance mutations.²⁵⁹ ASA disrupts quorum sensing (QS) in *Pseudomonas aeruginosa*, reducing virulence, biofilm formation, and motility by interacting with the LasR receptor, highlighting its potential as a QS inhibitor.²⁶⁰ Studies have shown its bacteriostatic activity against Gram-positive bacteria in rheumatic infections, although its efficacy against Gram-negative strains remains limited.²⁶¹ Additionally, aspirin reverses colistin resistance in multidrug-resistant *P. aeruginosa* and enterobacteria, significantly lowering MIC values and enhancing bactericidal effects.²⁶² Innovative ASA applications include ASA-doped polystyrene films, which demonstrate antibacterial activity against *Staphylococcus aureus*.²⁶³ Halogenated azo derivatives synthesized from aspirin exhibit enhanced activity against *E. coli* and *S. aureus*, outperforming ampicillin, supported by strong molecular interactions with bacterial proteins.²⁶⁴ In endocarditis models, ASA reduces *S. aureus* adherence to platelets and fibrin matrices, disrupting bacterial colonization.²⁶⁵ These findings collectively underscore aspirin's antibacterial potential and its promising role in overcoming antibiotic resistance and improving treatment outcomes.

Antiviral Effects of Aspirin

Aspirin exhibits antiviral effects by modulating host immune responses and inhibiting viral replication. In *Influenza A* infections, low-dose aspirin prevented endothelial dysfunction and improved fetal outcomes in pregnancy models.²⁶⁶ Combining aspirin with type-I interferon (IFN-I) for chronic hepatitis B (HBV) therapy enhanced IRF9 phosphorylation and IFNAR1 stability, achieving a functional cure in over 86% of cases.²⁶⁷ Aspirin demonstrated strong activity against *Influenza A*, rhinoviruses, and respiratory syncytial virus, although mechanisms against rhinoviruses remain unclear.²⁶⁸ In COVID-19, aspirin reduced thrombotic events and inflammation, with potential applications in resource-limited settings.²⁶⁹ In rotavirus infections, aspirin reduced viral replication and modulated gut microbiota composition,²⁷⁰ while in HIV, it showed limited impact on immune activation during antiretroviral therapy.²⁷¹ Aspirin inhibited *Influenza A* replication by targeting NF-κB signaling and blocking caspase activation.²⁷² The aspirin derivative APHS selectively inhibited HIV-1 reverse transcription.²⁷³ Long-term aspirin use reduced hepatocellular carcinoma (HCC) risk in chronic viral hepatitis patients,²⁷⁴ although it did not significantly affect mortality in H1N1 influenza cases.²⁷⁵ Additionally, aspirin inhibited *Cytomegalovirus* replication and reduced reactive oxygen species and NF-κB activation.²⁷⁶ Regular aspirin therapy also lowered HBV-related HCC risk by 29%.²⁷⁷

Antifungal Activities of Aspirin

Aspirin (ASA) exhibits significant antifungal properties, offering potential as a broad-spectrum antifungal agent. It inhibits the growth of *Candida albicans* and *Candida parapsilosis*, reduces tissue damage, and acts as a lipase inhibitor, impairing fungal lipase activity.²⁷⁸ ASA demonstrates potent antibiofilm activity, reducing biofilm formation in *C. albicans* by up to 95% via cyclooxygenase inhibition, making it an effective adjunct to conventional antifungals.²⁷⁹ It eradicates biofilms of various *Candida* species on surgical catheters, particularly *C. albicans*, which is highly sensitive to aspirin treatment.²⁸⁰ Photodynamic therapy combining ASA and ultraviolet light inhibits *Cryptococcus* growth by inducing mitochondrial damage, increasing reactive oxygen species, and reducing capsular gene expression.²⁸¹ Nitric oxide-releasing aspirin (NO-ASA)

enhances fluconazole's efficacy against resistant *C. albicans* biofilms by reducing adhesion, filamentous growth, and prostaglandin E2 synthesis.²⁸² ASA damages fungal cell walls by targeting dolichol phosphate mannose synthase 1 (DPM1), increasing surface hydrophobicity, and directly binding to DPM1 at the Ser141 site.²⁸³ Additionally, aspirin alters lipid metabolism in *Saccharomyces cerevisiae* and *C. albicans* by modulating DCI1 and OLE1 expression, contributing to its antifungal efficacy and offering novel perspectives for antifungal drug development.²⁸⁴

Aspirin and Its Therapeutic Efficacy in Other Diseases

Aspirin has shown promise in various non-inflammatory, non-cancerous conditions, expanding its therapeutic utility. For migraines, aspirin effectively reduces pain and inflammation, particularly when combined with metoclopramide.²⁸⁵ In Alzheimer's disease, its anti-inflammatory and antioxidant properties have been linked to reduced risk, with hazard ratios ranging from 0.76 to 0.81 over 1, 3, and 5 years post-ischemic stroke.²⁸⁶ However, further randomized trials are required to confirm these findings. In aspirin-exacerbated respiratory disease (AERD), patients experience more severe asthma exacerbations and poorer outcomes compared to aspirin-tolerant individuals, highlighting aspirin's variable effects in asthma subtypes.²⁸⁷ In cardiovascular disease (CVD) prevention, aspirin remains a cornerstone, especially for secondary prevention, though newer strategies like P2Y12 monotherapy offer lower bleeding risks.²⁸⁸ Aspirin therapy reduced hepatocellular carcinoma (HCC) incidence in non-alcoholic fatty liver disease (NAFLD) patients, with long-term users showing significant reductions in adjusted hazard ratios (aHR: 0.48).²³⁶ In stroke management, IST and CAST trials demonstrated that aspirin initiated within 48 hours reduced recurrent stroke and mortality without increasing hemorrhagic risk.^{289,290} For Kawasaki disease, high-dose aspirin in the acute phase reduces inflammation, while low-dose aspirin prevents thrombosis in children with coronary aneurysms.²⁹¹ Figure 5 illustrates aspirin's therapeutic versatility, with its effects spanning antibacterial, antiviral, antifungal, cardiovascular, and neurological diseases.

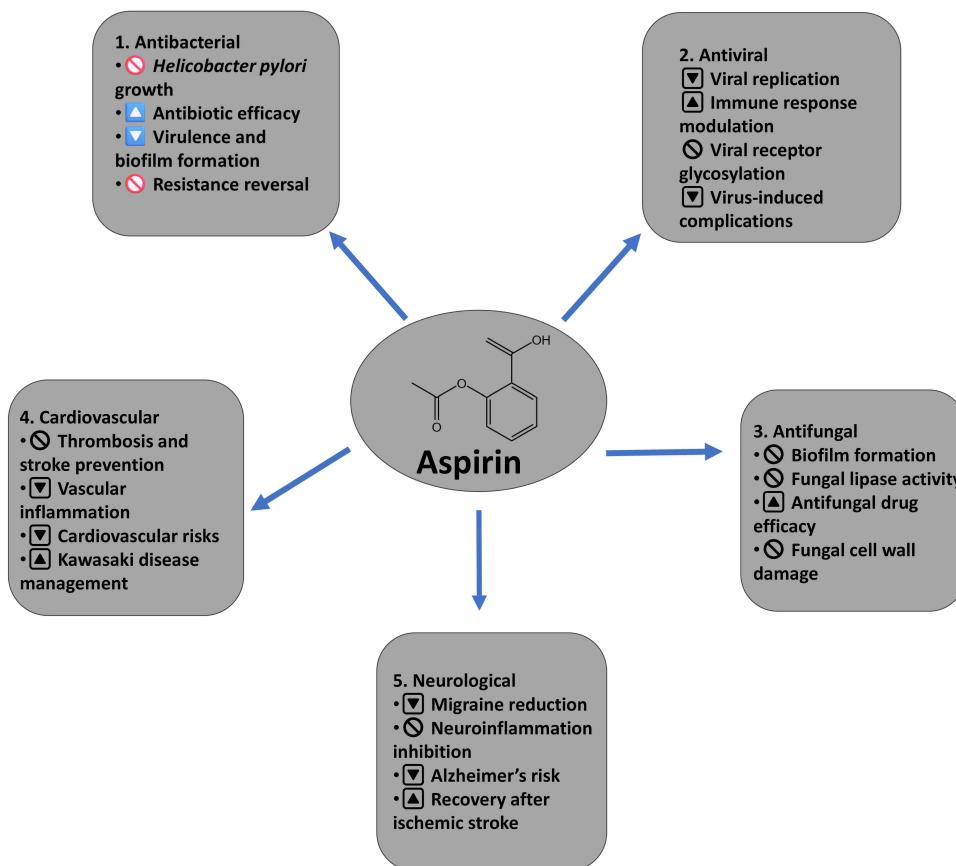


Figure 5 Overall Therapeutic Applications of Aspirin Across Multiple Diseases. This figure highlights aspirin's diverse therapeutic roles, including antibacterial, antiviral, antifungal, cardiovascular, and neurological effects. It inhibits microbial growth, enhances drug efficacy, modulates immune responses, and reduces inflammation across various systems. These multifaceted actions underscore aspirin's broad utility in managing infections, cardiovascular conditions, and neurodegenerative disorders.

Conclusion

Aspirin's established role in cancer therapy, through its modulation of COX-dependent and independent pathways, highlights its broad-spectrum anticancer potential. While conventional aspirin therapy faces challenges such as systemic toxicity and limited bioavailability, nanotechnology has emerged as a transformative solution. Advanced nanocarriers, including liposomes, solid lipid nanoparticles, and mesoporous silica nanoparticles, enhance aspirin's solubility, stability, and tumor-specific delivery. These systems enable controlled drug release, minimize off-target effects, and improve therapeutic outcomes. Combining aspirin-loaded nanoparticles with other bioactive molecules or chemotherapeutics offers synergistic effects, addressing treatment resistance and improving efficacy. The integration of nanotechnology thus elevates aspirin's role in precision oncology, paving the way for safer, targeted cancer therapies. Continued research and clinical trials will be crucial to optimizing these innovations and solidifying aspirin's place in next-generation cancer treatment strategies.

Data Sharing Statement

The authors declare that all the data supporting our findings in the study are available within the paper.

Consent for Publication

All authors consent to publication of this article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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