The Current Clinical Application Status and Pharmacological Mechanism of Aspirin

Chao Hu *

College of Life Sciences, Zhuhai College of Science and Technology, Guangdong, China

* Corresponding Author Email: 23huchao6@gmail.com

Abstract. Aspirin (acetylsalicylic acid), a long-standing drug, has evolved from an antipyretic and analgesic to a multi-purpose agent, especially in cardiovascular disease prevention. Recently, its potential has extended to cancer prevention, pregnancy complications, and neurodegenerative diseases, though debates on efficacy and safety persist. Current evidence shows limited net benefit of low-dose aspirin in primary cardiovascular prevention due to bleeding risks, while its role in colorectal cancer prevention varies by population, dose, and duration. New derivatives like NO-aspirin may reduce gastrointestinal toxicity, but require further study. Aspirin's mechanisms—beyond COX-1/2 inhibition—include possible effects on immune modulation and epigenetic regulation, though these are not yet fully understood. Its anticancer potential may involve enhancing tumor antigen presentation and modulating the tumor microenvironment. Clinical trials suggest limited benefit in preventing colorectal cancer recurrence post-surgery, except possibly in patients not treated with oxaliplatin. Gastrointestinal side effects remain a major concern, but strategies like PPI co-treatment or genotyping may reduce risks. This review highlights aspirin's prospects in precision medicine, emphasizing the need for genomic and epigenetic biomarkers to guide its use, and calls for further studies on non-COX pathways, AI-based risk assessment, and expanded clinical trials to optimize its role in complex disease management.

Keywords: Aspirin, Analgesia, COX-1/2 inhibition.

1. Introduction

Aspirin, one of the oldest synthetic drugs in human history, can be traced back to the use of willow bark in the treatment of pain by Hippocrates in Ancient Greece in the 5th century B.C. In the late 19th century, the successful synthesis of acetylsalicylic acid by the German chemist Felix Hoffmann, which was commercialized in 1899 by the Bayer Company, marked the birth of modern aspirin [1]. Initially widely used in clinical practice as an antipyretic and analgesic, its mechanism of action was honored with the Nobel Prize in the 1970s for the discovery of its inhibitory effect on cyclooxygenase (COX) by John Van), which initiated the revolutionary transformation of aspirin from a traditional analgesic to a preventive drug against cardiovascular disease (CVD). Today, aspirin has become the most widely used antiplatelet drug in the world, with more than 100 billion tablets consumed annually, but its clinical application still faces complex issues of efficacy and risk. Antiplatelets are the core value of aspirin. However, there are many controversial issues in the field of primary prevention. 2018 Many clinical trials have shown that low-dose aspirin (75-100 mg/d) significantly increases the risk of major bleeding in middle-aged and elderly populations without a history of CVD, although it reduces the risk of nonfatal infarction). Recent studies have revealed the potential value of aspirin in tumor control. In long-term studies, daily low-dose aspirin has been shown to reduce the incidence of colorectal cancer by 20-40%. Mechanistic studies have pointed out that its anticancer effects may be achieved by inhibiting COX-2-mediated prostaglandin synthesis and inducing apoptosis in tumor cells. However, 20-year follow-up data from the CAPP2 trial in 2021 showed that while aspirin reduced the risk of colorectal cancer in patients with Lynch syndrome, it did not have a significant effect on other cancers, suggesting that its anticancer effect is tissue-specific. Genome-wide association studies have identified COX-1 gene polymorphisms that may affect drug sensitivity. In addition, to reduce gastrointestinal toxicity, novel agents such as NO-aspirin have entered phase II clinical trials and initially showed a 50% reduction in bleeding risk. This paper will review the history of aspirin, its physicochemical properties, and the development of new drugs. By integrating

multidisciplinary evidence, this paper aims to provide a scientific basis for clinical decision-making and a theoretical framework for future research directions.

2. Pharmacological Mhanisms of Ation

2.1. Chemical Sucture and Parmacokinetics

Aspirin, also known as acetylsalicylic acid, is widely used in a variety of drugs. The molecular structure of aspirin is modified by acetylation of salicylic acid. The structure of the aspirin molecule is modified by acetylation of salicylic acid, and aspirin has unique pharmacological properties attributed to its acetyl group. The acetyl group can inhibit irreversible inhibition of COX through modification, which has selective and long-lasting effects, and the acetyl group can enhance lipid solubility and improve the efficiency of drug absorption in the gastrointestinal tract [1]. Aspirin is usually administered in one of four ways: orally, rectally, intravenously, or topically. The method of administration depends on the desired relief. Whereas oral is generally the optimal mode of administration; by oral administration, the acetyl group is hydrolyzed in a first-pass effect in the liver, which is further excreted through the kidneys. This process prolongs the duration of action of the drug and greatly reduces its immediate toxicity. It is eventually excreted through the kidneys. The blood concentration peaks within 30 minutes and the half-life is about 15-20 minutes, but its inhibitory effect on platelets lasts for 7-10 days, due to the lack of a nucleus for platelets to regenerate new COX enzymes [2].

2.2. COX Inhibition

The central mechanism of action of aspirin is inhibition by acetylation of COX enzymes, irreversibly inhibiting their activity. Aspirin is the only NSAID that irreversibly acetylates serine residues at the cyclooxygenase active site of bifunctional cyclooxygenases (COX-1 and COX-2). It has COX activity, both cyclizing arachidonic acid and adding 15-hydroxyl groups to form PGG2.The hydroxyl group of PGG2 is reduced to the hydroxyl group of PGH2 by a peroxidase enzyme, which uses a variety of compounds to provide the necessary electron pairs. The constitutive phenotypic expression of COX-1 is varied, but its most important contribution is found throughout the circulatory system, being present repeatedly in platelets throughout the body, endothelial cells and smooth muscle cells. The study also noted that aspirin does not block adenosine diphosphate (ADP)-mediated release of alpha particles that bind glycoproteins, fibrinogen, and vascular hemophilic factor. This suggests that aspirin does not completely inactivate platelets, but rather inhibits the synthesis of the most potent platelet activators and vasoconstrictors [3].

2.3. Other Potential Mechanisms

Recent studies have gradually revealed that the pleiotropic effects of aspirin are not only dependent on the classical COX inhibitory pathway, but may also be realized through a variety of non-COX-dependent molecular mechanisms. Among them, epigenetic regulation is an area that has received much attention in recent years. Studies have shown that aspirin can directly modify chromatin structure by acetylating histones (e.g., H3K9 and H3K27), thereby repressing the transcription of pro-inflammatory genes (e.g., TNF-α, IL-6, and COX-2). For example, in a model of chronic inflammation, aspirin treatment significantly reduced the expression level of IL-6 in macrophages, an effect that is closely related to its regulation of histone acetyltransferase (HAT) activity. This epigenetic regulatory mechanism may provide a new explanation for the long-term efficacy of aspirin in chronic inflammatory diseases such as rheumatoid arthritis or atherosclerosis. Further studies have shown that aspirin also exerts anti-cancer potential by inducing apoptosis in tumor cells. The mechanism involves the inhibition of COX-2-mediated prostaglandin E2 (PGE2) synthesis, which promotes tumor cell survival through activation of the PI3K/Akt and Wnt/β-catenin signaling pathways. For example, in colorectal cancer cell lines, aspirin treatment resulted in an increase in the Bax/Bcl-2 ratio, a decrease in mitochondrial membrane potential, and ultimately activation of the

caspase-3-dependent apoptotic pathway [4,5]. In addition, aspirin blocked the supportive effect of inflammatory factors in the tumor microenvironment (TME) on cancer cell growth by inhibiting NF-κB nuclear translocation. Notably, aspirin's modulation of the immune system should not be overlooked. It attenuates tissue damage in acute inflammatory responses by inhibiting the release of platelet-activating factor (PAF) and reducing the adhesion of neutrophils to the vascular endothelium. Preclinical studies have shown that aspirin pretreatment significantly reduced the intensity of pro-inflammatory cytokine storms while enhancing the immunosuppressive function of regulatory T cells (Treg) in a sepsis model. This finding provides potential theoretical support for its use in autoimmune diseases such as systemic lupus erythematosus [6].

3. Clinical Applications

3.1. CVD

After a large number of experiments in recent years, low-dose aspirin for secondary prevention of CVD has been widely recognized as effective. This is because it inhibits platelet aggregation, thereby reducing the risk of recurrent arterial thrombosis. Conclusive evidence of aspirin's benefit in secondary prevention comes from a meta-analysis of these trials, which showed that the aspirin group had a reduced risk of cardiovascular events and all-cause mortality and a 21% lower risk of reinfarction compared with placebo in more than 10,000 patients with myocardial infarction. However, in the area of primary prevention, in the randomized British Men's Doctors (BMD) trial, which was not placebo-controlled, 500 mg of aspirin per day did not reduce the incidence of all-cause vascular mortality, nonfatal myocardial infarction, or stroke, but it did result in a significant reduction in confirmed transient ischemic attacks, an increase in disabling strokes, and an increased risk of GI bleeding and intracranial bleeding, compared with no aspirin. The risk of gastrointestinal bleeding and intracranial hemorrhage is increased by 30%-40% [4]. Three large clinical trials in 2018 suggested that aspirin, when used for the primary prevention of CVD, reduces the risk of nonfatal infarction by 12% but significantly increases the risk of major bleeding by 30%-40%. Therefore, current guidelines emphasize the need for careful weighing of benefits and risks based on individualized assessments rather than broad recommendations. Future studies should further refine the criteria for stratifying high-risk populations to optimize the precise use of aspirin in prevention strategies.

3.2. Analgesia and Anti-inflammation

As a conventional NSAID, aspirin exposure to the vasculature triggers the production of 15-epi-LXA4 by acetylating COX-2 in endothelial cells or circulating leukocytes, which in turn induces the synthesis of nitric oxide (NO) by both eNOS and iNOS pathways [4]. Ultimately, aspirin-induced NO mediates the anti-inflammatory effects of aspirin in the microcirculation by negatively regulating leukocyte-endothelial cell interactions. And through aspirin reduces prostaglandin synthesis by inhibiting COX-2, which in turn leads to pain relief [5].

3.3. Other Potential Mechanisms

In recent years, the clinical use of aspirin has broken out of its traditional domain and its pleiotropic mechanisms have shown potential in areas such as cancer prevention and intervention in pregnancy complications. Evidence for the benefits of aspirin comes from many sources: its effects on biological mechanisms associated with cancer; the results of a number of randomized trials and outcome data from many observational studies. In addition, the biological mechanisms that lead to reduced metastatic spread of cancer and thromboembolic complications are the result of the biological effects of aspirin, distinct from, and possibly independent of, the mechanisms associated with mortality [7]. Thus, aspirin may have value in the treatment and care of patients independent of its effect on mortality. However, the efficacy and risks under different indications need to be analyzed together with evidence from specific studies. The role of aspirin in cancer prevention has received much

attention, but there is significant variation in research findings. Epidemiological data suggest that long-term (≥5 years) daily low-dose aspirin (75-100 mg/d) reduces colorectal cancer incidence by 20%-40% by a mechanism that may be related to inhibition of the COX-2/PGE2 pathway, induction of DNA repair, and modulation of the TME. For example, the 2025 University of Hong Kong study showed that aspirin (dose >100 mg/d for ≥10 years) in patients with type 2 diabetes mellitus reduced the risk of pancreatic cancer incidence by 31% and the risk of death by 57%, suggesting dose- and time-dependent effects. However, the ASCOLT trial, published in The Lancet in 2025, demonstrated that treatment with 200 mg of aspirin daily for 3 years failed to significantly reduce the risk of recurrence in the postoperative adjuvant treatment of patients with colorectal cancer (5-year disease-free survival 77.0% vs. 74.8%, HR=0.91), with subgroup analyses suggesting only a possible potential benefit in patients who did not receive oxaliplatin chemotherapy.3 This suggests that that the anticancer effects of aspirin may be tissue-specific or population-selective, and that future screening of subgroups for benefit by biomarkers (e.g., PIK3CA mutations, COX-2 overexpression) is warranted. In the area of pregnancy complications, the use of aspirin in obstetrics has expanded from preeclampsia prevention to improvement of placental insufficiency. Several guidelines recommend low-dose aspirin (81 mg/d) daily from 12 weeks of gestation in high-risk pregnant women (e.g., antiphospholipid syndrome, history of preeclampsia) to reduce the risk of preterm labor by 20%-30% by inhibiting the production of placental vascular thromboxane A2 and promoting endothelial nitric oxide release to improve blood flow. A Finnish study further found a 40% reduction in the incidence of fetal growth retardation after aspirin administration in early pregnancy in patients with abnormal uterine arterial flow, suggesting that it exerts a protective effect by regulating placental vascular remodeling.

4. Side Effects and Safety

Although aspirin has a wide range of clinical applications, its side effects and the safety of long-term use need to be given great attention. Gastrointestinal toxicity is the most common adverse reaction, mainly manifested as acid reflux, abdominal pain and even gastrointestinal bleeding, especially in long-term high-dose (≥1 g/d) use or the combination of Helicobacter pylori infection, the risk of which is significantly elevated. In addition, the antiplatelet effect of aspirin may lead to bleeding tendencies, such as rhinorrhea, subcutaneous petechiae, or intracranial hemorrhage, and the risk is higher in elderly patients and those with comorbid hepatic or renal disease. Other potential risks have been revealed in recent studies. For example, long-term use may exacerbate the deterioration of renal function in patients with chronic kidney disease (CKD) by inhibiting prostaglandin synthesis leading to decreased renal blood flow. Aspirin use remains a decision that should involve thoughtful discussion between clinicians and patients because of the need to weigh cardiovascular and possible cancer prevention benefits against bleeding risk, patient preference, cost, and other factors. The ARRIVE data must be interpreted and used in the context of other studies, which tend to show primarily reductions in myocardial infarction with lesser effects on total stroke, including ischemic and bloody rhagic stroke [8]. The overall decision to use aspirin for cardiovascular effects should be made with the help of a clinician because of the complex calculations required to balance all the potential benefits and risks. In addition, allergic reactions, manifesting as asthma, urticaria, or even anaphylaxis, may occur in approximately 5%-10% of patients, and are particularly common in those with comorbid nasal polyps or chronic respiratory disease. Of note, the effects of aspirin on the fetus are controversial, and although low doses (81 mg/d) used in high-risk pregnancies may prevent preeclampsia, use in late pregnancy may increase the risk of intracranial hemorrhage in the newborn, and strict guidelines for the use of medications during pregnancy need to be followed.

5. Current Research and Challenges

5.1. Reassessment of Cardiovascular Primary Prevention

The place of aspirin in the primary prevention of CVD has been debated in recent years. Three large trials in 2018 (ARRIVE, ASCEND, ASPREE) showed that while low-dose aspirin (75-100 mg/d) reduced the risk of nonfatal infarctions by 12%, it increased the risk of major hemorrhage by 30%-40%, and that aspirin doses of less than 75 mg/day were more effective than high doses are more effective because low doses have no effect on prostacyclin, a platelet anticoagulant and vasodilator that causes fewer gastrointestinal complications [9]. Systemic bioavailability of oral aspirin is necessary for vascular endothelial inhibition of prostacyclin synthesis, whereas platelet inhibition of thromboxane A2 synthesis occurs in the portal (precursor) circulation. Based on a meta-analysis of randomized studies, direct comparisons of aspirin <75 mg daily and >75 mg did not show significant differences in the prevention of vascular events in high-risk patients. Comparing aspirin to controls, the risk of major extracranial hemorrhage was similar for all aspirin doses <325 mg per day (ratio 1.7 (95% confidence interval 0.8-3.3) for <75 mg; 1.5 (1.0-2.3) for 75-150 mg; and 1.4 (1.0-2.0) for 160-325 mg). - 2.0) for 160-325 mg. altered platelet function in diabetic patients, but it is not clear how this might affect the cardioprotective outcome of aspirin dosing in the diabetic population. The net benefit was not significant, particularly in the elderly population. Based on this, the 2023 ACC/AHA guidelines recommend its use only for those with a 10-year atherosclerotic CVD (ASCVD) risk of ≥10% and a low risk of bleeding, and emphasize the need to refine population stratification in conjunction with biomarkers (eg, high-sensitivity C-reactive protein).

5.2. Mechanisms and Controversies of Cancer Prevention

Aspirin has a complex mechanism of anticancer action; in addition to classical COX-2/PGE2 pathway inhibition, recent studies have found that it enhances DNA damage repair through epigenetic regulation (e.g., histone H4K16 acetylation), thereby reducing mutation accumulation. Epidemiologic data suggest that long-term (≥5 years) low-dose aspirin use reduces colorectal cancer risk by 40%, but there is heterogeneity in the preventive effect on breast or prostate cancer. For example, the ASCOLT 2025 trial showed that aspirin use in postoperative colorectal cancer patients failed to significantly reduce the risk of recurrence, suggesting the need to screen for subgroups of benefit in conjunction with molecular characteristics of the tumor (e.g., PIK3CA mutations) [10].

6. Conclusion

This paper systematically sorted out the pharmacological mechanism of action of aspirin, the current status of its clinical application and its safety controversy. Studies have shown that aspirin exerts its antiplatelet and anti-inflammatory effects through irreversible inhibition of COX-1/COX-2, and at the same time extends its pleiotropic effects with the help of non-classical pathways, such as epigenetic regulation (e.g., histone acetylation) and immunomodulation (inhibition of PAF release). In clinical application, its core value is still focused on secondary prevention of CVD, while the net benefit of primary prevention needs to be assessed individually due to the elevated risk of bleeding; emerging areas such as cancer prevention and intervention for pregnancy complications are promising, but there is significant heterogeneity in efficacy, which needs to be combined with molecular markers (e.g., PIK3CA mutation, COX-2 overexpression) to accurately screen the beneficiary population. In terms of safety, gastrointestinal toxicity and bleeding risk remain major limitations, but the development of novel agents (e.g., NO-aspirin) offers potential solutions to balance efficacy and toxicity. The significance of this study lies in the integration of multidisciplinary evidence that redefines the changing role of aspirin from a traditional analgesic to a multi-targeted therapeutic agent. Echoing the core issue of "versatility and controversy" raised in the introduction, this paper reveals the "double-edged sword" characteristics of aspirin in different disease scenarios through mechanistic analysis and comparison of clinical data, providing a scientific framework for clinical decision-

making in terms of risk-benefit trade-offs. This provides a scientific framework for risk-benefit trade-offs in clinical decision-making. For example, in response to the controversy of cancer prevention, the present study puts forward the hypothesis of "tissue-specific effect", which emphasizes the need to optimize the drug regimen through the characteristics of the TME rather than generalization strategies.

In addition, the in-depth exploration of epigenetic regulatory mechanisms lays a theoretical foundation for the development of novel derivatives with stronger targeting properties (e.g., histone modification-specific drugs). Future research should focus on the following directions: first, to establish precise medication models through genomics and epigenetic markers (e.g., COX-1 polymorphisms, H3K9 acetylation levels) to achieve individualized risk stratification; second, to accelerate the development of novel formulations, such as the use of nanocarriers to enhance the targeting of drugs or the design of pre-drugs to reduce the toxicity of metabolism; third, to carry out cross-disciplinary cooperation, integrate artificial intelligence and multi-omics Third, interdisciplinary cooperation, integration of artificial intelligence and multi-omics data to dynamically predict the potential benefits and risks of long-term drug use. Aspirin's 100-year history proves that only through mechanism innovation and technology integration can we break through the traditional limitations and reshape its multidimensional value in modern medicine.

References

[1] Ricciotti E, FitzGerald G A. Aspirin in the prevention of cardiovascular disease and cancer [J]. Annual Review of Medicine, 2021, 72: 473 – 495.

[2] Vane J R, Botting R M. The mechanism of action of aspirin [J]. Thrombosis Research, 2003, 110: 255 – 258.

[3] Rao P, Knaus E E. Evolution of nonsteroidal anti-inflammatory drugs (NSAIDs): cyclooxygenase (COX) inhibition and beyond [J]. Journal of Pharmacy and Pharmaceutical Sciences, 2008, 11: 81s – 110s.

[4] Montinari M R, Minelli S, De Caterina R. The first 3500 years of aspirin history from its roots: a concise summary[J]. Vascular Pharmacology, 2019, 113: 1 – 8.

[5] Gilroy D W. The role of aspirin-triggered lipoxins in the mechanism of action of aspirin [J]. Prostaglandins, Leukotrienes and Essential Fatty Acids, 2005, 73: 203 – 210.

[6] Zhou J, Zeng W, Zeng Y, Li Y, Xiao Z, Zou J, Peng L, Xia J, Zeng X. Anticancer and anti-inflammatory mechanisms of NOSH-aspirin and its biological effects [J]. Computational and Mathematical Methods in Medicine, 2022: 4463294.

[7] Methods in Medicine CAM. Retracted: Anticancer and anti-inflammatory mechanisms of NOSH-aspirin and its biological effects [J]. Computational and Mathematical Methods in Medicine, 2023: 9861539.

[8] Gaziano J M, Brotons C, Coppolecchia R, Cricelli C, Darius H, Gorelick P B, Howard G, Pearson T A, Rothwell P M, Ruilope L M, Tendera M, Tognoni G; ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial [J]. Lancet, 2018, 392 (10152): 1036 – 1046.

[9] Soodi D, VanWormer J J, Rezkalla S H. Aspirin in primary prevention of cardiovascular events [J]. Clinical Medicine Research, 2020, 18 (2–3): 89 – 94.

[10] Hybiak J, Broniarek I, Kiryczyński G, Los L D, Rosik J, Machaj F, Sławiński H, Jankowska K, Urasińska E. Aspirin and its pleiotropic application[J]. European Journal of Pharmacology, 2020, 866: 172762.