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Aspirin: Classical Molecular Pharmacology, Off-Label; Repurposing Potentials and Benefit-Risks

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Abstract. Aspirin is a century-old classic nonsteroidal anti-inflammatory drug (NSAID) that has been clinically used as an antipyretic, an analgesic, an anti-inflammatory and an anti-rheumatic. The principle clinical activity is its ability to inhibit cyclooxygenase (COX), which blocks the production of prostaglandins, reducing pain, fever and excessive inflammatory response in rheumatic and inflammatory disorders. In addition, progress in pharmacology and molecular biology has shed further light on the mechanisms of action of aspirin and highlighted the potential for aspirin to be used as a drug repurposing target. In addition to the well-known COX pathway, aspirin has many non-canonical bioactivities, such as anti-tumor activity, intervention in metabolic disorders, neuroprotection in neurodegenerative diseases, COX independent anti-inflammatory activity and regulation of cellular anti-senescence activity. These novel pharmacological properties have been supported by a wealth of pre-clinical data and retrospective observational clinical evidence but remain to be unequivocally confirmed with large scale prospective randomized controlled trials. In this review, the traditional molecular actions of aspirin, the newly reported therapeutic indications during the last five years, and the critical safety concerns of gastrointestinal mucosal damage and systemic bleeding will be described, and unresolved issues regarding optimal doses, target patient groups and the intricate benefit-risk ratio will be analyzed. Future research avenues are also explored such as novel targeted formulations and strategies of personalized medicine, tailored to individual genetic traits and clinical phenotypes. This book offers a theoretical foundation for aspirin-oriented translational research and offers rational evidence-based guidance to extend its clinical therapeutic role.

Keywords: aspirin, cyclooxygenase, pharmacological mechanism, drug repurposing, antithrombosis

1. Introduction

1.1. Brief development history of aspirin

Aspirin (acetylsalicylic acid) is derived from folk medicines used for centuries. Willow bark was noted by Hippocrates as a remedy for pain, fever, and inflammation, and it contains salicin, the natural precursor to salicylic acid. Salicylic acid was first isolated in 1828 from willow bark by Johann Buchner and later converted into salicylic acid. However, salicylic acid was toxic to the

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stomach and, though potent, was not very useful in clinical practice. In 1897, Bayer chemist Felix Hoffmann acetylated salicylic acid to synthesize acetylsalicylic acid. The anti-inflammatory, analgesic, and antipyretic properties were preserved in this new compound, and stomach damage was reduced. Bayer trademarked the name "Aspirin" and released the drug commercially in 1899. For almost 70 years, it was used as a pain reliever more than any other medication. In the late 20th century, a breakthrough occurred: researchers discovered that aspirin irreversibly blocks the activity of cyclooxygenase, thereby inhibiting platelet aggregation and blood clotting. Low-dose aspirin has been used routinely as a preventive treatment for heart attacks and ischemic strokes since the 1970s. Today, aspirin continues to have two clinical uses: as an anti-inflammatory drug and as a cardiovascular protective agent

1.2. Brief development history of aspirin

Aspirin, IUPAC-named acetylsalicylic acid, bears two ortho-positioned functional groups on. Its benzene ring: an acetyl ester group (-$OCOCH_3$) and a carboxylic acid group (-COOH), as illustrated in Figure 1. As shown in the figure, its benzene ring has two functional groups attached to it my extending outwards, with an ester group at the left and a carboxyl group above the ring. Chemically labile, aspirin readily hydrolyzes into salicylic acid and acetic acid in aqueous and physiological media [1]. For pharmacokinetics, oral aspirin is largely absorbed in the upper gastrointestinal tract (stomach and small intestine). A fraction is hydrolyzed within the intestinal wall during first-pass metabolism, whereas unhydrolyzed acetylsalicylic acid enters systemic circulation [1]. Its major metabolite salicylic acid distributes widely in tissues and is finally cleared by renal excretion [1].

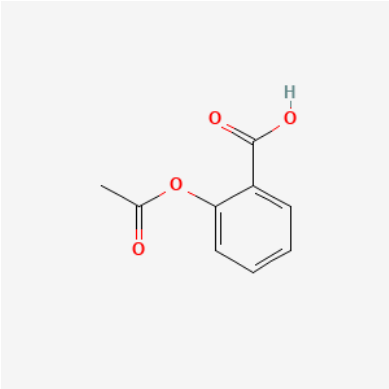


Figure 1. Two-dimensional chemical structure of aspirin (CID 2244) [2]

For unbuffered formulations, absorption can be rapid, and typically peak plasma concentration is achieved in 30-40 minutes. Most of the aspirin that is absorbed is rapidly metabolized by plasma esterases and mucosal enzymes into its primary active metabolite, salicylic acid. Very little of the intact acetylsalicylic acid is in the blood. Salicylic acid is highly plasma albumin bound. It is widely distributed throughout the body tissues and may cross the placenta. Metabolism takes place in the liver through conjugation for production of inactive metabolites. Mostly renal elimination: urinary pH has a significant effect on the excretion rate; with alkaline urine, it increases salicylate elimination. The plasma half-life of the parent aspirin is short (~15 min), and that of salicylic acid is dose-dependent, ranging from 2-3 h when administered at low anti-platelet doses to 12-20 h at high anti-inflammatory doses.

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1.3. Persistent research value of the century-old drug and the framework of this review

It is a drug that has been around for a century – aspirin is a prime example of a century-old drug. pharmaceutical agent that has been used for many purposes beyond its originally recognized antipyretic, analgesic, and anti-rheumatic properties. Over the last 120+ years of clinical use, there are still many new biological activities of aspirin that are being discovered, both in the preclinical and clinical settings. Ongoing research is active in tumor chemoprevention, modulation of metabolic disease, effects on neuropsychiatric diseases, anti-infection activity, and intervention in inflammaging. However, several critical uncertainties remain conflicting findings for primary cardiovascular prevention; yield for cancer-related repurposing remains unclear; interpatient variability in response to the drugs; tradeoffs regarding safety issues with prolonged use. The lack of resolution in these issues continues to drive interest in this classic drug for translational research. Consequently, the structure of this review is outlined as follows: The classical pharmacological actions and the underlying molecular mechanisms of aspirin are discussed in the next chapter, which includes covalent inhibition of cyclooxygenase-1/2, antipyretic-analgesic, anti-inflammatory-anti-rheumatic, and anti-platelet antithrombotic effects. Following on, the content summarizes the recent advances in repurposing applications such as malignancy chemoprevention, adjuvant therapy, possible applications in metabolic-endocrine disorders, neurological disease research, and other novel bioactivities, then reviews and discusses the most serious adverse reactions and drug safety issues such as gastrointestinal injuries, bleeding disorders, special hypersensitivity events, and the benefit-risk relationship over the long-term low dose administration. Finally, it discusses some of the major existing controversies as well as new directions for future research including primary prevention populations and uncertainties surrounding dosing; opportunities for targeted formulations that might be safer; precision personalized medicine; and the future of clinical translation of novel indications.

2. Classical pharmacological effects and molecular mechanisms of aspirin

2.1. Covalent inhibition mechanism of cyclooxygenase

2.1.1. Tissue distribution and physiological functional differences between COX-1 and COX-2

There are two major COX (cyclooxygenase) isozymes, and the two types are different to each other in both structure and functions. COX-1 is a housekeeping constitutive enzyme that is highly expressed in gastric mucosa, renal tissue, and circulating platelets. In the gastric epithelium, prostaglandins (made by COX-1) promote mucus and bicarbonate production, ensure proper blood flow to the stomach, and protect the gastric mucosa from gastric acid. In renal tissues, these prostaglandins regulate renal blood flow and electrolyte balance, thus maintaining renal function. COX-1 is expressed in platelets and is required for the synthesis of TXA2 (thromboxane A_2) in response to blood vessel injury to ensure normal physiological hemostasis and prevent minor bleeding.

By comparison, COX-2 is hardly detectable in most healthy resting tissues. It has several regulatory. sequences in its gene promoter that are responsive to inflammation. The COX-2 gene is rapidly and acutely transcribed at the site of infection or tissue damage by pro-inflammatory mediators such as interleukin-1 and tumor necrosis factor-α. A new enzyme, COX-2, produces large amounts of prostaglandin. They decrease the threshold of peripheral sensory nerves for activation and enhance the perception of pain, induce local vasodilation and tissue swelling, and act on the

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hypothalamus to reset the thermoregulatory set-point and induce fever. This distinct expression and physiological function of the two isoforms is the molecular explanation as to why aspirin is effective yet has unwanted side effects. They have different variations in the enzyme active site structure, which results in variation in response to aspirin treatment [3].

2.1.2. Characteristics of irreversible acetylation modification by aspirin

Aspirin, unlike most NSAIDs, acts by covalent acetylation of the serine residues of the COX active site [4]. The modification causes a physical blocking of the enzyme active site for the arachidonic acid substrate and leads to permanent inactivity of the enzyme. Platelets have no nuclei and therefore cannot transcribe genes to make new COX-1 protein. This means that aspirin's inhibition remains during their entire 7–10-day circulation. In comparison, nucleated cells can regain the ability to synthesize prostaglandins by expressing and translating newly produced molecules of COX. Aspirin's main metabolite, salicylic acid, is unable to perform acetylation and only weakly inhibits reversibly [5].

2.2. Antipyretic and analgesic effects

Pyrogenic cytokines stimulate the production of PGE_2 in the hypothalamus and reset the body's temperature set-point [6]. Aspirin enters the CNS and inhibits central COX-2 activity, which leads to a drop in PGE_2 concentration and helps to alleviate fever. Its primary effect is in the peripheral tissue, preventing nociceptor sensitization to pain mediators and relieving mild–moderate somatic pain, for analgesia. Central effects play a small role in overall pain relief [6].

Aspirin, used for antipyretic and analgesic usages, varies from 300 to 1000 mg per dose. This dose range treats common conditions such as headache, muscle pain, and infection-associated fever. Pharmacological responses are dose-dependent, with more symptom relief gained for higher doses and greater gastrointestinal adverse risk. Rather than a treatment of the underlying cause of the disease, aspirin serves as a symptomatic treatment.

2.3. Anti-inflammatory and anti-rheumatic effects

Inflammatory signals trigger rich local expression of COX2, which results in the production of. pro-inflammatory prostaglandins that are responsible for swelling, heat, and joint tenderness [7]. These lipid-mediator levels are decreased by aspirin, and so are inflammatory symptoms. However, aspirin cannot block upstream cytokine signaling; it is only able to block downstream prostaglandin production, so aspirin is not able to reverse the autoimmune pathological progress of the roots [7].

High doses of aspirin (3 to 6 g daily, given in divided doses) are indicated for anti-rheumatic management [8]. With this dose, the half-life of salicylate is significantly prolonged because the metabolism is saturated by the drug and unable to process any more. The risks associated with high-dose therapy are significant, such as gastric erosion, tinnitus, and salicylate intoxication. Modern clinical recommendations would favor the use of other NSAIDs and consider high-dose aspirin to be a second-line drug because of safety concerns [9].

2.4. Antiplatelet aggregation and antithrombotic effects

Besides vascular injuries, platelet COX-1 can catalyze the synthesis of TXA2, which is a potent lipid messenger that amplifies platelet recruitment and the formation of thrombus. Aspirin irreversibly acetylates the platelet COX-1 and nearly eliminates the biosynthesis of TXA2. The

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aggregation capacity of platelets will remain suppressed until the novel platelets enter the circulatory system.

Daily low-dose aspirin, which ranges from 75 to 100 mg per dose, irreversibly inhibits platelet COX-1 and only-from a low and impotent effect, suppresses systemic COX-2. It is given to patients who have suffered a myocardial infarction or ischemic stroke as a secondary prevention measure to reduce the risk of further ischemic events. Due to the potential for serious bleeding complications, using aspirin from a long span requires further careful consideration and balancing between the risks and the benefits.

3. Researching progress on novel repurposing applications of aspirin

3.1. Chemoprevention and adjuvant therapy for malignancies

Colorectal cancer is the most well-validated tumour model for aspirin repurposing. Long-term low-dose aspirin was associated with decreased incidence of colorectal adenoma and carcinoma and improved survival. However, aspirin should not replace routine colonoscopy screening, and the protective effect was not uniform across molecular tumor subgroups.

Aspirin suppresses the production of tumour-promoting PGE_2 via COX-dependent pathways. Several COX-independent pathways have been identified, including the inhibition of NF-κB, promotion of tumour-cell apoptosis, and modulation of tumour-microenvironment immune cells; the contribution of these mechanisms may differ from each other given each cancer type also has a subtle difference

Clinical evidence for the treatment of breast, liver, and pancreatic cancer is rather inconsistent. While some retrospective cohort studies reported a protective or beneficial effect for long-term aspirin users, large-scale randomized clinical trials are needed to confirm the observed results. Moreover, the included patients varied in terms of the doses and treatment regimens, which maybe the cause of the different outcomes of the studies.

Biomarkers such as Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) at the mutation status are being investigated to identify populations that may derive the most anti-cancer benefit from aspirin. Initial clinical evidence suggests a treatment benefit for specific PIK3CA subgroups; however, robust clinical biomarker qualification strategies for routine practice are lacking.

3.2. Potential applications in metabolic and endocrine disorder

Preclinical data and small-sample clinical trials indicate that aspirin can partially alleviate. Polycystic ovary syndrome by reducing inflammatory pathways and steroid hormones [9]; however, more extensive clinical studies are required for promoting and widespread worldwide a step further, which is beneficial for all platinum-sensitive ovarian cancer (PSOC) patients.

Aspirin-mediated inflammatory pathway down-regulation might be improved alongside with the sensitivity of peripheral insulin. Observational studies have identified an association between aspirin and metabolic risk factors. However, aspirin's role in the treatment of patients with type 2 diabetes has not been consistently supported. Since the main reason for type 2 diabetes is that despite insulin being produced, it is not bound to the liver and therefore does not respond. Nowadays, the predominant medication for this disease is mostly metformin, the role and function of aspirin in the treatment of type 2 diabetes are yet to be determined.

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3.3. Novel research directions in neurological diseases

3.3.1. Neuroinflammation suppression and antidepressant potential

Animal experiments confirm that aspirin suppresses microglia-induced neuroinflammation and exerts. antidepressant-like behavioral effects [10]. These preclinical hints are insufficient for recommending aspirin in the treatment of psychiatric diseases, although positive human clinical trial results are awaited. Overactive microglia can lead to chronic neuroinflammation and damage to neurons, and to a loss of normal neurotransmitter metabolism, all of which are well established to be linked to the development of depression and other psychiatric conditions and are closely associated with the microglial state in brain tissue. Aspirin has anti-inflammatory effects and can prevent or inhibit inflammatory pathways, leading to a decrease in the production of pro-inflammatory cytokines and thus improving stress-induced depressive behaviors in animal models. These promising preclinical results underscoring the neuroprotective and psychotropic properties of aspirin are encouraging, but translating this promise to clinical application is very limited. It has yet to be proven to be effective and safe for the treatment of psychiatric diseases on a large scale and with good quality in humans. Thus, aspirin cannot be used as a preventive medicine or a therapeutic agent in depression, and more extensive and detailed clinical studies are needed to assess its clinical application value.

3.3.2. Controversies and advances in Alzheimer's disease prevention

Preliminary research suggests aspirin could have several protective effects against Alzheimer's disease (AD). In addition to its classical COX-dependent anti-inflammatory effect, aspirin also has anti-inflammatory properties in the central nervous system (CNS) that include suppression of neuroinflammation, ease of amyloid-β clearance, inhibition of tau hyperphosphorylation, and reduction of oxidative stress in brain tissue. These mechanistic observations have led to great interest in repurposing aspirin for risk reduction of AD. However, clinical results are still conflicting. Several retrospective observational cohort studies have found possible links between low-dose aspirin use and reduced risk for dementia. In contrast, multiple future randomized controlled trials have not been able to establish consistent cognitive protective effects. The existing trials have several limitations, including the fact that they included patients with heterogeneous inclusion criteria, different aspirin dosage regimens, varying follow-up periods, and other confounding factors such as the presence of baseline cardiovascular comorbidities. Currently, there remains strong clinical evidence for the widespread use of aspirin for primary or secondary prevention of Alzheimer's disease. Aspirin for primary prevention of dementia is not advised as there are potential risks of gastrointestinal and haemorrhagic side effects.

3.4. Other emerging potential applications

Basic research at an in-vitro level reports on aspirin's anti-infective and antiviral effects, based on its anti-inflammatory mechanisms. However, these findings are purely laboratory-based, and thus, there is currently insufficient evidence for its clinical application in the treatment of any infections.Aspirin can partially block age-associated low-grade inflammation in pre-clinical models [11]. In human studies, mostly observational, associations were found, but causality and optimised regimens for anti-ageing purposes remain to be established.

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4. Adverse reactions and medication safety risks of aspirin

4.1. Mechanisms and risk factors of gastrointestinal injury

Gastric COX-1 downregulation leads to decreased production of cytoprotective prostaglandins, increasing the risk of developing mucosal erosions and ulcers [12]. The older increased the blood flow in mucosa and epithelial repair are reduced, and high dose increases the exposure of the mucosa to harmful agents. NSAIDs suppress COX-1 systemically which decreases cytoprotective prostaglandins. H. pylori lead to local inflammation, compromises mucosa barrier and works synergistically with NSAIDs. Locally NSAIDs cause direct damage to epithelial cells, systemically the gut is weakened, allowing acid and pepsin to cause gastroduodenal damage

4.2. Bleeding risks: gastrointestinal hemorrhage and intracranial hemorrhage

Irreversible inhibition of platelet function leads to enhanced bleeding risk, manifested in major. bleeding complications such as gastrointestinal hemorrhage and rare but serious intracranial hemorrhage [13]. Patients presenting with a bleeding diathesis or receiving concomitant anticoagulant therapy and elderly individuals are at higher risk and more vulnerable to bleeding on chronic aspirin use.

4.3. Special adverse reactions: aspirin-exacerbated respiratory disease, Reye's syndrome

Aspirin-induced respiratory disease is characterized by the development of asthma and rhinitis following aspirin ingestion caused by altered metabolism of arachidonic acid [14]. Another serious adverse effect of aspirin is Reye's syndrome which manifests as hepatic encephalopathy that mostly affects children with aspirin use during viral infections. Therefore, considering the potential threats it might pose, aspirin use in children should be controlled and inhibited.

4.4. Benefit-risk balance principle for long-term low-dose administration

The benefit-risk balance principle for long-term, low-dose administration of aspirin requires. careful consideration. The risk of developing an ischemic event should be weighed against possible adverse effects for each patient, and medication should be prescribed only if benefits outweigh potential harms. Patients on long-term therapy with low-dose aspirin should periodically undergo medication re-evaluation.

5. Conclusion

As a century-old non-steroidal anti-inflammatory drug, aspirin primarily produces classical anti-inflammatory effects, such as antipyretic, analgesic, and anti-rheumatic effects, and anti-platelet aggregation effects, by means of covalent cyclooxygenase acetylation. Due to the different pharmacological effects caused by aspirin at different dosages, the clinical application of this drug also varies significantly: moderate doses are used to reduce fever and relieve pain, large doses are used to alleviate the swelling caused by rheumatism, and low-dose long-term use can prevent the occurrence of blood clots in the cardiovascular and cerebral vessels. In addition, there is growing pre-clinical and clinical evidence that supports the diverse roles of aspirin in tumor prevention, metabolic regulation, and modulation of neuroinflammation, through both COX-dependent and

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COX-independent mechanisms. However, most of these potential indications for aspirin are just emerging, and conflicting evidence limits its broader clinical use for now.

Gastrointestinal damage and bleeding and special hypersensitivity reactions are the main factors. that limit the use of aspirin. The principle of rational use of this drug should be to make a benefit-risk assessment for each individual patient. Although there are controversies in the field about the selection of populations for use, dosage settings, and the role of biomarkers, aspirin has huge research value for the time being. More clinical trials are needed in the future for the rational use of this classic anti-inflammatory drug, and new safer drugs derived from aspirin are also of great research value. Even after more than 120 years of clinical history, aspirin continues to function as an inspiring model for repurposing old medicines for modern medical demands.

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