JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

# ASPIRIN: THE LONG LIVING DRUG

**[1]Om Dixit, [2]Janak Jansari, [3]Shubham Savaliya, [4]Dr. Vaibhav Patel**

[1, 2, 3]Doctor of Pharmacy 5th Year Students
[4]Professor Pharmacology & Pharmacy Practice
Saraswati Institute Of Pharmaceutical Sciences, Dhanap. Gandhinagar, India

*Abstract :* Salicylates have been around since the turn of the century. It has the properties of anti -inflammatory, anti pyretic, analgesic, anti-platelet. It belongs to the drug class of NSAIDS. It acts by irreversibly binding to the COX-1 & COX-2 enzymes. In order for clinicians to direct patient care in treating stated conditions as a member of the interprofessional team, this activity describes the indications, mechanism of action, routes of administration, significant adverse effects, contraindications, and monitoring for salicylic acid. used for treating, preventing and managing the disease of multiple system. Which include various disease such as cardiovascular, stroke, pain, headaches, cancer, inflammatory diseases

**(Keywords:** Aspirin, Acetylsalicylic acid, NSAIDs (Nonsteroidal anti-inflammatory drugs), Mechanism of action, Pharmacokinetics, Pharmacodynamics, Antiplatelet effects, Dosing regimens, Adverse effects, Drug interactions.**)**

## Introduction

Willow tree bark has been used to make salicylates. It has been documented that the Sumerians utilised willow tree extracts as pain relievers as far back as 4,000 years ago. [1] Hippocrates used it to treat fever and discomfort. Even during childbirth, he used tea made from it to alleviate his agony. Reverend Edward Stone conducted the first-ever clinical experiment of its sort in 1763 to examine the efficacy of willow bark powder in the treatment of fever. The effects of the powdered willow bark were explored for acute rheumatism about 100 years later.Professor Johann Buchner used the Latin word salicin, which means willow, in 1828. In 1829, Henri Leroux isolated it and utilised the crystalline form to cure rheumatism. The Heyden Chemical Company was the first to commercially mass-produce salicylic acid in the 1800s. It wasn't until 1899 that acetylsalicylic acid, a modified form, was registered and put on the market by Bayer under the brand name aspirin. Although it has been around since the turn of the century, its true manner of operation was not discovered until the late 1970s. Some of the indications for aspirin use are as follows:[2] [3]

- Angina pectoris
- Angina pectoris prophylaxis
- Ankylosing spondylitis
- Cardiovascular risk reduction
- Colorectal cancer
- Fever
- Ischemic stroke
- Ischemic stroke: Prophylaxis
- Myocardial infarction
- Myocardial infarction: Prophylaxis
- Osteoarthritis
- Pain
- Revascularization procedures: Prophylaxis
- Rheumatoid arthritis
- Systemic lupus erythematosus

## Objectives:

- Describe the method by which salicylic acid works.
- Describe any possible side effects that salicylic acid may have.
- Go over the many conditions for which salicylic acid is advised as a treatment.
- Outline the significance of enhancing care coordination within the multidisciplinary team to guarantee the secure application of salicylic acid.

## Chemistry Of Aspirin

Salicylic acid is a benzene ring that has both a carboxylic acid (COOH) group and a phenol (HO) group. Dr. Felix Hoffman, a German chemist at Friedrich Bayer and Co., focussed on the phenol group instead of the carboxylic acid group, and on August 10,

1897, he succeeded in acetylating the phenol group to create pure stable acetylsalicylic acid (ASA) for the first time.[4][5] Arthur Eichengrün, Carl Duisberg, and Wilhelm Siebel were among the scientists who encouraged and inspired him in this work.[4][5][6] The pharmaceutical industry and aspirin were both created by Dr. Hoffman's discovery, which was the first time a medication had been created synthetically.[4] Professor Heinrich Dreser, Head of the Pharmacology Institute at Bayer, tested Hoffman's finding on himself first after realising its significance before conducting successful animal tests and human clinical trials.[4]
On February 1st, 1899, the new substance was given the name and registered as aspirin. The letters "A" and "spir" stand for acetyl and the first portion of Spirea ulmaria (Meadowsweet), two plants that are sources of salicylic acid, respectively.

## Mechanism Of Action

Cyclooxygenase-1 (COX-1) is inhibited by aspirin. It modifies cyclooxygenase-2's (COX-2) enzymatic activity.[7] Aspirin binding to this enzyme is irreversible, in contrast to other NSAIDs (ibuprofen/naproxen), which bind reversibly.[8] Additionally, it permanently prevents thromboxane A2 on platelets, blocking platelet aggregation.[9][10]
Researchers believe that the arachidonic acids are transported into the lipoxygenase route as a result of the COX pathway being blocked. Modifying prostaglandin-endoperoxide synthase (PTGS2), also known as COX-2, causes the creation of lipoxins, the majority of which are anti-inflammatory, which in turn causes the production of anti-inflammatory lipoxins. Aspirin-triggered lipoxins, aspirin-triggered resolvins, and aspirin-triggered maresins are the names of these substances.
Aspirin can be administered via the oral, rectal, and intravenous (IV) route.
It is available in different doses, the lowest being 81 mg, also called a baby aspirin.

- Tablet: 325 mg, 500 mg
- Delayed-release tablet: 81 mg, 325 mg, 500 mg, 650 mg
- Chewable: 81 mg
- Suppository: 60 mg, 120 mg, 200 mg, 300 mg, 600 mg
- Intravenous: 250 mg, 500 mg

## Pharmacokinetics[11]

The formulation state affects how well aspirin is absorbed from the GI system. As opposed to pills, it is quickly absorbed when ingested as a liquid mixture. Salicylic acid is produced during its hydrolysis. There is a small therapeutic window for salicylic acid. If kept within that certain range, it has the necessary anti-inflammatory effects.
The small intestine is where aspirin absorption is pH sensitive. For the same pH range, the small intestine absorbs more nutrients than the stomach. The intestinal absorption of aspirin is greater than the stomach absorption of the drug at pH 3.5 or 6.5. At pH 6.5, aspirin is not absorbed by the stomach.
Salicyluric acid and salicyl phenolic glucuronide are produced in order to eliminate salicylates via two different mechanisms. Raising the pH of the urine can accelerate the clearance of salicylic acid through the kidneys. As they raise urine pH, medications like antacids can boost renal clearance. The blood-placental barrier can be crossed by it. Breast milk also expresses it.

## Pharmacodynamics[11]

With the dose of 160 to 325 mg of aspirin, COX inhibition can be attained to over 90%. These effects typically continue for 7 to 10 days, which is the same amount of time as a platelet lives. It is possible to block prostate cyclin by using greater doses. The blood vessel's endothelial cells experience this inhibition.

## Adverse Effect

According to numerous metanalyses, aspirin seems to increase the risk of bleeding and gastrointestinal issues while also lowering the risk of serious adverse cardiovascular events in people with diabetes who do not already have heart disease.[12][13][14][15] Aspirin's most frequent adverse reaction is gastrointestinal discomfort, which can range from gastritis to gastrointestinal bleeding.[16]

### Hypersensitivity

NSAIDs frequently cause hypersensitivity in the general population. It ranges from 1% to 2%. The signs and symptoms might range from a simple rash to angioedema and anaphylaxis. The prevalence of these allergy symptoms in people with asthma or chronic rhinosinusitis may reach 26%. The aspirin triad is defined as the presence of nasal polyps, respiratory tract inflammation, and eosinophilic inflammation. Because of the inflammation of the upper and lower respiratory mucosa, this illness is now known as NSAID-exacerbated respiratory disease (NERD).

### Syndrome Reye

Reye syndrome was originally mentioned in 1963 and is named after the Australian pathologist Dr. R.D. Reye. With a mortality rate of between 30% and 45%, it is a rare but devastating illness. It is a type of encephalopathy brought on by fatty alterations in a liver that is otherwise healthy. A viral upper respiratory tract infection in children and concurrent aspirin use to treat a fever make up the clinical scenario of Reye syndrome. The first injury to the liver and the brain is assumed to be mitochondrial damage as a result of the viral disease that came before. The second dose of aspirin or comparable medications completes the condition. Because of increased knowledge and the substitution of acetaminophen for aspirin when treating a child's fever, the incidence has significantly decreased.[17] Although there is evidence linking aspirin to Reye syndrome, other writers contend that at the time of diagnosis, salicylate levels were not routinely examined, biopsies were not taken, and genetic/inborn metabolic abnormalities were not excluded. Intracerebral Bleeding In comparison to placebo, aspirin raises the incidence of cerebral haemorrhage (RR = 1.65; 95% CI, 1.06 to 5.99).

## Contraindications:

Aspirin should not be taken by people who are allergic to ibuprofen due to cross-reactivity. Patients who have asthma or previous bronchospasm associated with NSAIDs should exercise caution.

Patients who currently have gastritis or peptic ulcer disease are more at risk for gastrointestinal bleeding when taking aspirin. If there is concurrent alcohol use or if the patient is on warfarin, there is still a risk of bleeding even in the absence of these conditions. All salicylates should be avoided by patients with inborn coagulopathies, such as haemophilia. Aspirin should not be taken if you have acquired diathesis, such as when you have dengue fever or yellow hemorrhagic fever.

Patients who lack the enzyme that breaks down glucose-6-phosphate are at risk of developing acute intravascular hemolytic anaemia. These hemolytic episodes might be triggered by a variety of reasons. One such known cause is aspirin. To prevent Reye syndrome in children with viral infections, avoid giving them aspirin.[17]

## Toxic Dose and Therapeutic Index

Aspirin's salicylate therapeutic medication levels range from 150 to 300 mcg/mL. Threat Levels: in excess of 300 mcg/mL 1 to 3 hours following the dose Five to seven days for steady state. For therapeutic doses, aspirin plasma levels can vary from 3 to 10 mg/dL to as high as 70 to 140 mg/dL for acute toxicity. Levels should be monitored four hours after administration and then every two hours until maximum levels are attained due to the delayed absorption of some preparations. Individualised care must be provided depending on both levels and symptomatology. Most of the time, aspirin levels do not require monitoring. Serum medication levels and serum creatinine levels at baseline are required for several illnesses, such as adult or paediatric rheumatoid arthritis, Kawasaki disease, or arthritis/pleurisy.

## Toxicology

There are numerous symptoms that aspirin toxicity patients may experience. Tinnitus, vertigo, fatigue, nausea, and vomiting are only a few of the signs of moderate poisoning.[18] Hyperthermia, tachypnea resulting in respiratory alkalosis, large anion gap metabolic acidosis, hypokalemia, hypoglycemia, seizures, coma, and cerebral edoema are some of the warning signs and symptoms of more severe toxicity. Cardiopulmonary edoema, which results from pulmonary edoema, frequently causes death. [19][20]

Salicylate concentration, acid-base status, volume status, electrolytes, GI decontamination, airway protection and respiratory status, and increased elimination are taken into consideration when treating salicylate poisoning. [21]

Salicylate levels in serum can be impacted by the degree of exposure, the formulation type, co-ingestions, comorbidities, and clinical condition of the patient. Of all of these, acid-base state has the most potential to affect how the body processes the medicine. Therefore, it is advised to evaluate trajectory using the initial and following levels. Salicylate levels may be reported in various ways by different laboratories. Salicylate concentration units must be taken into consideration. The conversion looks like this:

- 100 milligrams per deciliter (mg/dL) equals
- 1000 milligrams per liter (mg/L), or
- 7.24 millimoles per liter (mmol/L)

To establish a decrease in absorption and demonstrate a decline in salicylate levels, serial salicylate levels must be drawn. High anion gap metabolic acidosis and pulmonary alkalosis are brought on by aspirin. Salicylic acid is added, and lactic acid is produced as a result of the uncoupling of oxidative phosphorylation, which results in anaerobic respiration, which results in a significant anion gap. The direct stimulation of the respiratory centre is what causes the respiratory alkalosis. Acidemia makes symptoms worse. Both ionised and non-ionized salicylate are present in blood. Salicylate becomes more lipophilic and can penetrate the central nervous system (CNS) more deeply when acidemia converts it from its ionised to unionised forms. Even when serum glucose levels are normal, volume status and electrolyte monitoring are crucial because brain glucose utilisation rises in the context of aspirin toxicity. Since acidemia is exacerbated by hypokalemia, supplementing may be necessary.

Bicarbonate drips (3 ampules of 50 meq/50 ml for a total of 150 meq in 1000 ml of D5W) can be used to alkalize urine. However, this could make hypokalemia worse, thus potassium supplementation needs extra attention.

Because there are extended-release medications on the market, they are advised for both acute and chronic intake together with activated charcoal and/or colon irrigation. One must take extra precautions to prevent aspiration pneumonia in the presence of deteriorating mental status. When a person's mental state deteriorates or suffers an acute lung injury, airway protection may be necessary. To prevent CNS toxicity, an alkaline pH must be maintained. To avoid carbon dioxide ($CO_2$) retention, this can be accomplished by increasing the minute ventilation. During intubation, a pH of no more than 7.5 can be achieved by bicarbonate drips.

Toxic salicylate poisoning can be effectively treated with hemodialysis. Dialysis is an effective method for removing the free fraction once the protein-boun

Salicylate is not effectively removed by peritoneal dialysis.

The following are hemodialysis indications: [22]

- 100 mg/dL of aspirin in acute ingestions, with or without symptoms
- 40 mg/dL of aspirin in chronic ingestions, with or without symptoms
- Any neurotoxicity (coma, seizures, tinnitus) at any level
- Renal failure (since the kidneys are required for the drug's clearance).
- Acute lung edoema
- Cardiovascular dysfunction, such as volume overload

Haemodialysis restores the internal acid-base and electrolyte balance in addition to removing the medication from circulation.

## Improving Nursing Results

The over-the-counter drug aspirin is frequently used in paediatric overdoses. The drug needs to be stored out of children's reach in a closed cabinet. All members of the interprofessional healthcare team should be aware of when patients are taking aspirin and should monitor and counsel the patient to optimise therapeutic outcomes and prevent any potential salicylic acid side effects due to

its widespread availability, potential adverse effects, therapeutic uses, and potential interactions. All clinicians (MDs, DOs, NPs, and PAs), nurses, and chemists make up this interprofessional team. For the patient to receive the best healthcare possible, including how aspirin is used, all of these professionals must coordinate their activities, have access to the same patient information, and share information openly. [Level 5]

## Medicinal Use With Dose [2]

Cardiovascular disease (secondary prevention)

- Adult: 75 mg daily

Secondary prevention of deep-vein thrombosis (in patients who decline continued anticoagulation treatment) Secondary prevention of pulmonary embolism (in patients who decline continued anticoagulation treatment)

- Adult: 75 mg daily, alternatively 150 mg daily

Management of unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI)| Management of ST-segment elevation myocardial infarction (STEMI)

- Adult: 300 mg, chewed or dispersed in water

Suspected transient ischaemic attack

- Adult: 300 mg once daily until diagnosis established

Transient ischaemic attack (long-term treatment in combination with dipyridamole)
Ischaemic stroke not associated with atrial fibrillation (in combination with dipyridamole if clopidogrel contra-indicated or not tolerated)
Ischaemic stroke not associated with atrial fibrillation (used alone if clopidogrel and dipyridamole contra indicated or not tolerated)

- Adult: 75 mg once daily

Acute ischaemic stroke

- Adult: 300 mg once daily for 14 days, to be initiated 24 hours after thrombolysis or as soon as possible within 48 hours of symptom onset in patients not receiving thrombolysis Atrial fibrillation following a disabling ischaemic stroke (before being considered for anticoagulant treatment)
- Adult: 300 mg once daily for 14 days

Following disabling ischaemic stroke in patients receiving anticoagulation for a prosthetic heart valve and who are at significant risk of haemorrhagic transformation

- Adult: 300 mg once daily, anticoagulant treatment stopped for 7 days and to be substituted with aspirin

Following coronary by-pass surgery

- Adult: 75–300 mg daily

Mild to moderate pain/Pyrexia

- Adult: 300–900 mg every 4–6 hours as required; maximum 4 g per day

Acute migraine

- Adult: 900 mg for 1 dose, to be taken as soon as migraine symptoms develop

Prevention of pre-eclampsia in women at moderate or high risk

- Adult: 75–150 mg once daily from 12 weeks gestation until the birth of the baby

Mild to moderate pain (dose approved for use by community practitioner nurse prescribers)| Pyrexia (dose approved for use by community practitioner nurse prescribers)

- Child 16–17 years: 300–600 mg every 4–6 hours as required, maximum 2.4 g per day without doctor's advice
- Adult: 300–600 mg every 4–6 hours as required, maximum 2.4 g per day without doctor's advice

## References


1. Tawfeek N, Mahmoud MF, Hamdan DI, Sobeh M, Farrag N, Wink M, El-Shazly AM. Phytochemistry, Pharmacology and Medicinal Uses of Plants of the Genus Salix: An Updated Review. Front Pharmacol. 2021;12:593856. [PMC free article] [PubMed]
2. Liu N, Mathews A, Swanson J, Mhaskar R, Mathews A, Ayoubi N, Mirza AS. Aspirin use for cardiovascular disease prevention in the uninsured population. SAGE Open Med. 2020;8:2050312120938224. [PMC free article] [PubMed]
3. Drugs for osteoarthritis. Med Lett Drugs Ther. 2020 Apr 20;62(1596):57-62. [PubMed]
4. Jack DB. One hundred years of aspirin. The Lancet 1997:350: 437-39
5. Elwood P. Aspirin yesterday, aspirin today, aspirin tomorrow: a history of prophylactic aspirin. 2017 International Aspirin Foundation
6. Schrör K. Acetylsalicylic acid. 2016 Wiley
7. Zimmermann P, Curtis N. The effect of aspirin on antibiotic susceptibility. Expert Opin Ther Targets. 2018 Nov;22(11):967-972. [PubMed]

8. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development; Bethesda (MD): Aug 16, 2021. Willow Bark. [PubMed]
9. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development; Bethesda (MD): Aug 16, 2021. Choline Magnesium Salicylate. [PubMed]
10. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development; Bethesda (MD): Aug 16, 2021. Salsalate. [PubMed]
11. Christiansen M, Grove EL, Hvas AM. Contemporary Clinical Use of Aspirin: Mechanisms of Action, Current Concepts, Unresolved Questions, and Future Perspectives. Semin Thromb Hemost. 2021 Oct;47(7):800-814. [PubMed]
12. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development; Bethesda (MD): Sep 20, 2021. Aspirin. [PubMed]
13. Handa O, Takayama S, Mukai R, Suyama Y, Majima A, Fukui A, Omatsu T, Naito Y. A review of the mechanism and prophylaxis of acetyl salicylic acid-induced injury of the small intestine. Free Radic Res. 2018 Dec;52(11-12):1266-1270. [PubMed]
14. Kosinski P, Sarzynska-Nowacka U, Fiolna M, Wielgos M. The practical use of acetylsalicylic acid in the era of the ASPRE trial. Update and literature review. Ginekol Pol. 2018;89(2):107-111. [PubMed]
15. Navaratnam K, Alfirevic Z, Pirmohamed M, Alfirevic A. How important is aspirin adherence when evaluating effectiveness of low-dose aspirin? Eur J Obstet Gynecol Reprod Biol. 2017 Dec;219:1-9. [PubMed]
16. Weltermann T, Schulz C, Macke L. Effect of frequently prescribed drugs on gastric cancer risk. Best Pract Res Clin Gastroenterol. 2021 Mar-Apr;50-51:101741. [PubMed]
17. Mount M, Toltzis P. 50 Years Ago in The Journal of Pediatrics: Aspirin and Reye Syndrome. J Pediatr. 2020 Jul;222:192. [PubMed]
18. Blanca-Lopez N, Perez-Alzate D, Canto G, Blanca M. Practical approach to the treatment of NSAID hypersensitivity. Expert Rev Clin Immunol. 2017 Nov;13(11):1017-1027. [PubMed]
19. Kristensen DM, Mazaud-Guittot S, Gaudriault P, Lesné L, Serrano T, Main KM, Jégou B. Analgesic use - prevalence, biomonitoring and endocrine and reproductive effects. Nat Rev Endocrinol. 2016 Jul;12(7):381-93. [PubMed]
20. Patrignani P, Patrono C. Cyclooxygenase inhibitors: From pharmacology to clinical read-outs. Biochim Biophys Acta. 2015 Apr;1851(4):422-32. [PubMed]
21. McEvoy L, Carr DF, Pirmohamed M. Pharmacogenomics of NSAID-Induced Upper Gastrointestinal Toxicity. Front Pharmacol. 2021;12:684162. [PMC free article] [PubMed]
22. Dizon K, Ng PCK, Battistella M. A retrospective study of antithrombotic therapy use in an outpatient haemodialysis unit. J Clin Pharm Ther. 2021 Oct;46(5):1387-1394. [PubMed]