

A Review On The Oldest Wonder Drug: Aspirin

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Abstract: Aspirin is one of the most broadly utilized medications in the world. It was discovered as an anti-inflammatory agent in 1874. Since then many other benefits of this drug like antipyretic, anti-platelets, anticancer etc have been demonstrated in animals and humans by various researcher's time to time. Studies have demonstrated that a small amount of Aspirin for the over 50s can increase life since Aspirin decreases the danger of numerous diseases related with aging. It is one of the oldest drugs used to treat inflammation and cardiovascular diseases in humans, however it is still the first line drug to treat these diseases till date. The present article focuses on physicochemical and pharmacological properties of aspirin along with a brief overview of recent ongoing researches on this molecule all over the world.

Index Terms: Acetylsalicylic acid, Meadowsweet, prostaglandins, salicylates, Heparanase

1 INTRODUCTION

Aspirin (Acetyl Salicylic Acid) is a standout amongst the most generally utilized therapeutic substances because of its pain relieving, antipyretic and anti-inflammatory properties. In spite of the acceleration in the improvement of new non-steroidal anti-inflammatory drugs (NSAIDs), Aspirin is still a drug of choice by most of the physicians in the treatment of rheumatic arthritis. Besides, because of its anti-thrombotic properties, Aspirin is presently recommended in low dose in the counteractive action and treatment of cardiovascular illnesses, strokes and as a scatter related with platelet agreeability [1]. It acts by obstruction of prostaglandin production and COX-II inhibitor. Aspirin use has been appeared to lessen the rate and mortality of human tumors, particularly colon malignancy. Orally administered Aspirin requires high and successive dosing in light of the fact that it experiences broad presystemic metabolism. Additionally, long term and unending oral Aspirin is related with genuine gastrointestinal (GIT) side effects like peptic ulcers, GIT bleeding etc [2]. Currently, numerous epidemiological, clinical, and test considers have appeared long haul utilization of Acetyl Salicylic Acid can essentially decrease frequency of cancer, decrease the danger of metastasis process of cancerous tissues, and death rate due to cancers [3],[4],[5],[6],[7]. In spite the fact that patients taking aspirin have advantages of decline in cancer formation chances, but the mechanism of action still not clear. Past understandings will in general quality the antitumor capability of Acetyl Salicylic Acid to the hindrance of cyclooxygenase-2 enzyme, that may up regulate in different malignancy cells [8],[9]. Of note, expanding proof have proposed but Acetyl Salicylic Acid may display anticancer impacts within cyclooxygenase-free way. The consequences of inconsistency are that the focuses requisite to apply these impacts in malignancy tissues were altogether greater than that required to hinder the movement of cyclooxygenase-1 and cyclooxygenase-2, proposing the ramifications of additional possible targets [10,11]. However, investigations based on cell studies revealed that Acetyl Salicylic Acid restrains growth of cell, actuates capturing process of tumour cell apoptosis independent of COX-2 expression level [12– 14].

Acetyl Salicylic Acid can make malignant growth cells sensitive to TRAIL-induced apoptosis via COX-2-autonomous component [15]. Patients based investigations affirmed that the advantage of Acetyl Salicylic Acid seems random with cyclooxygenase-2 enzyme hindrance however with different proteins, for example, PIK3CA and HLA class I antigen [16],[17],[18]. Accordingly, this is a significance which portray the Aspirin's spectrum in malignant growth cell line and show its relationship towards Aspirin's anticancer activity.

2. History

The historical backdrop of Aspirin returns a huge number of years to the early employments of plant's-based preparations that contain salicylate. Maclagan [19] utilized Salicin, the noxious constituent obtained from common white willow, effectively in 1874 as antipyretic, to relieve pain and aggravation of rheumatic fever. Additionally, in 1874, the Salicylic acid-based blend was figured by Kolbe and his partners and prompted the establishing of the Heyden Chemical Company. The achievement of salicylic acid incited the pharmaceutical production house of Frederick Bayer to effectively look for a subsidiary of practically identical or better efficacy to salicylic acid. Arthur Eichengrün, of Bayer in 1895, appointed this assignment to a youthful scientist Felix Hoffman. Hoffman additionally had own explanations for requiring an increasingly adequate salicylic acid subordinate; as his father was using salicylic acid to treat complications of his joint inflammation and had as of late found that without vomiting, he could never again take the medication. Induced then by obedient love just as by devotion to his activity, Hoffman sought through the literature and found a method for acetylating the hydroxyl group on the benzene ring of salicylic acid to frame acetylsalicylic acid. After starting research tests, Hoffman's father was given the medication; it was pronounced effective. The name "Aspirin" was given to the new medication by the Bayer's main pharmacologist, named Heinrich Dreser [20], who was trying to find a particular name that couldn't in any way, shape or form be mistaken for salicylic acid. There are two records which reveal the decision of Dreser's toward deciding the name; a few experts keep up that the medication's name was after St Aspirinius, an early Neapolitan diocesan which was the supporter holy person to treat cerebral pains. An increasingly trite clarification is that the name was gotten from *Spiraea*, which is the Linnaean name for the plants to which meadowsweet belongs. Salicylaldehyde is the main constituent present in Meadowsweet, which can be oxidized to salicylic acid. As indicated by this clarification, the salicylic acid present in *Spiraea* progressed toward becoming "Spirsaure" in German. "Acetylsalicylic acid" prepared from

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acetylation of *Spirsaúre* which leads to naming of Aspirin.

3. Physicochemical properties

Acetyl salicylic acid is a white crystalline powder having somewhat bitter taste yet in moist air it is progressively hydrolysed and builds up the vinegar like scent of acetic acid. It is slightly soluble in water (4600 mg/L at 25⁰ C) yet completely soluble in alcohols. In aqueous medium, Acetyl Salicylic Acid is stable between pH 2-4, while metastable at 4-8 pH range and stability highly reduced below at pH 2 or higher than pH 8. When stored in saturated form on pH of 5 to 7, Acetyl Salicylic Acid gets hydrolysed within a week at 25⁰ C. On heating above 140⁰ C, it emanates harsh smoke and exhaust [1], [21].

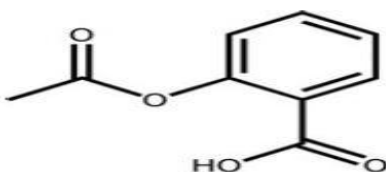


Fig. 1. Chemical Structure of aspirin:

TABLE 1

PHYSICOCHEMICAL PROPERTIES RELATED TO ASPIRIN [21]

Physical appearance	A white crystalline powder.
Solubility profile	Slightly soluble in water
Empirical Formula	C ₉ H ₈ O ₄
Molecular Weight	180.159 g/mol
Melting Point	About 135 ⁰ C
Chemical Name	2-Acetyloxybenzoic acid
CAS	50-78-2
Log P	1.19
pKa value	3.49 at 25 ⁰ C
Protein Binding	80-85%
Category	NSAID
Storage	Aspirin should be kept in a tightly closed container, protected from liq

4. Method of Analysis for acetylsalicylic acid and salicylic acid

According to United State Pharmacopoeia's high-performance liquid chromatography technique is employed in the concurrent dosage of acetylsalicylic acid and salicylic acid in tablets [22]. Experimental assessment of this technique indicates that the scheme adequacy parameters (primarily classification and amplifying criterion) were not accurate. This chromatographic scheme is also not very sensitive in any linear analytical process. This condition is not acceptable in any circumstances. Although numerous methods were used like change in mobile phase or changing the columns lengths etc. but these were not found to be sufficient [23]. The kinetic degradation of acetylsalicylic acid was followed by the deacetylation reactions and the formation of salicylic acid.

Molecular intake results in the UV spectrum were acquired in seven concentrations of the standard graph of the salicylic acid and acetyl-salicylic acid spikes. The selectivity was evaluated by means of spectral associations before, during and after the proper retention of the material. The first step was taken by the experimental outline: i) determination of the concentration range of interest in considering the method application, to assess the linearity of analytical response to the analysed substances. The anticipated sample concentrations were selected closely to the medium size; ii) standard solution analysis in seven cluster levels, similarly distributed, prepared in triplicate, autonomous from each stage vii) injection of solution in random pattern. Data analyses with common minimum blocks were performed [24]. Analysis for a standard solution of 0.302 mg / mL during a 180-minute study was carried out on acetylsalicylic acid stability, by ultraviolet-based chromatography, and is checked to form linear salicylic acid, tenor (percent)=0.0005 t + 0.0302, R²=0.9935. The result was an assessment of the standard solution. This result suggests that the sample should be injected immediately after its preparation, to ensure the reliability of analytical results in the samples with a salicylic acid tenor that is near the tolerated limit (3.0%). In linear regression equation of salicylic acid formation trend, an increase of 0.043% in the free salicylic acid limit can be verified after twenty five minutes (sample preparation). The spectra of molecular absorption in the ultraviolet range against the ultraviolet spectra of molecular absorption have been compared to the respective acetylsalicylic and Salicylic acids standards by means of a pureness and selection of the peaks of acetylsalicylic and Salicylic acid. Chromatographic analysis of acetylsalicylic acid used four important parameters (enlargement parameter 1.2; numbers of plate 2485; retention parameter 1.6; as well as standard deviation 0.3%) while in case of Salicylic acid, the factor was enlargement parameter 1.26, resolution 5.06, retention parameter 2.72, numbers of plate 4177, standard deviation 0.2% were found to be satisfactory. The selectivity was evaluated by means of spectral associations before, during and after the proper retention of the material. The linear work range was found to be 0.21-0.39 mg/mL for acetylsalicylic acid while 6.3-11.7 µg/mL for Salicylic acid. The quantification and detection limit for Salicylic acid was found to be 0.23 and 0.69 µg/mL, respectively. In the analytical curve, the values of correlation coefficients (r) for Salicylic acid and acetylsalicylic acid were found to be 0.9988 and 0.9995 respectively. So, on the basis of above discussion, this method could be used for quantitative determination of acetylsalicylic and salicylic acids in tablets [25].

5. Pharmacological action

In the NSAID's category, Acetyl Salicylic Acid is most ordinarily utilized. It is helpful for relieving the pain related to minor musculoskeletal ailments, for example, bursitis, tendinitis, synovitis, myositis, and myalgia. It may likewise be utilized as tranquilizer and to treat cerebral pain. It can be utilized in the treatment of inflammatory illness, for example, intense rheumatic fever, rheumatoid joint pain, osteoarthritis, and certain rheumatoid variations, for example, ankylosing spondylitis, Reiter's disorder, and psoriatic joint pain. In any case, different NSAIDs are generally supported to treat the perpetual disorders in light of its downward side effects related to gastro-intestinal symptoms. Aspirin is utilized for treating the recurrence of cardiac diseases [21].

5.1 Mechanism of action

In spite of the fact that Acetyl Salicylic Acid is highly active pharmacologically, as it quickly hydrolysed to salicylic acid just after its absorption, salicylate anion that represents the vast majority of the anti-inflammatory action of the medication. The unrivalled pain-relieving association of aspirin contrasted and sodium salicylate infers that aspirin has a characteristic action that isn't absolutely logical by its transformation to salicylic acid. Aspirin hinders COX-1 to a lot more prominent degree in comparison to COX-2 enzyme; while COX-1 specific activity was found for sodium salicylate [26]. This, joined with the capacity of aspirin to acetylate proteins, may represent a portion of the helpful and toxicological contrasts among aspirin and alternate salicylates.

5.2 Pharmacokinetics

After oral ingestion, Aspirin get absorbed from GI and the smaller intestinal area (disintegration of formulation take place at basic pH of gut area). Rectal ingestion of the aspirin is moderate and inconsistent; however, it is a helpful route of administration for spewing youngsters. Aspirin must be avoided from in youngsters and adolescents (<15 years old) with varicella (chickenpox) or flu to prevent Reye's disorder [27]. Aspirin (with the exception of diflunisal) passes the Blood brain barrier and the placenta and are absorbed through flawless skin (particularly methyl salicylate). Aspirin is a prodrug that in the stomach, in the intestinal mucosa, in the blood and primarily in the liver is transformed into salicylate. Salicylate is the active metabolite responsible for most anti-inflammatory and analgesic impacts. In some people the gastrointestinal intolerance to salicylate led to the development of enteric coating formulations. Salicylate spreads quickly into the reservoir of body fluid. In plasma, it combines to albumin. The unbound proportion improves with increased complete plasma salicylate levels. The oral bioavailability of aspirin is 69%, while Volume of distribution (Vd), Clearance (CL) and half-life ($t_{1/2}$) was found to be 10.5 L, 39 L/h and 0.25 h respectively. The protein binding capacity of aspirin differs from the plasma concentration. In the serum, binding of salicylic acid under 100 g/mL, 90 to 95% is protein bound; at 100 to 400 g/mL, 70 to 85% is protein bound; and at concentration more prominent than 400 g/mL, 20 to 60% is protein bound. The concentration of salicylate in plasma is related to mitigating action (200– 300 g/mL) is around 6 times which is expected to deliver relieving of pain. At these higher concentrations, salicylate metabolism is decreased, bringing about a more drawn out t_{50} for the API. Its response is an outcome of saturated catalyst frameworks which utilize salicylates. The serum t_{50} for salicylic acid has been assessed to be 3-6 hours at the lower (pain relieving) dose and 15 to 30 hours at the higher amount. Aspirin to salicylic acid hydrolysis rate is not restricted to its dose because there is no change in absorption of aspirin have been recorded in patients and ordinary people [28]. At a dose of 650 mg/day, Acetyl Salicylic Acid is dissociated in to salicylate and acetic acid with the help of enzyme esterases. Salicylate is changed over by the liver to water-solvent conjugates that are quickly cleared by the kidney, bringing about end with first-order kinetics and a serum half-life of 3.5 hours. At anti-inflammatory dose (>4 g/day), the hepatic metabolic pathway ends up saturated, and zero- order kinetics is examined, with the medication having a half-existence of 15 hours or more. The saturability of the liver-based compounds need treatment for a few times. Being a

natural acid, salicylates are released within urine and also influence uric acid excretion, at lower amount of Acetyl Salicylic Acid, uric acid discharge is reduced, while at high dosages, uric acid discharge is expanded. Both hepatic and renal capacity ought to be checked intermittently in those getting long term, high-dose aspirin treatment, and aspirin ought to be maintained at a safe distance from in patients with a creatinine clearance of under 10 mL/min [27].

5.3 Pharmacodynamics

As already indicated, acetyl salicylic acid quickly biotransforms into salicylate, the effective metabolite. There is therefore a very small half-life for aspirin. On the other hand, salicylate is metabolized primarily in the liver. The above metabolism happens mainly through hepatic combination to glycine and sometimes glucuronic acid, with metabolism. The main route is the saturable combination of glycine. About 90% of salicylate is metabolized in this way with small amounts of aspirin. The other paths with less permission are more crucial as the maximum capacity of this significant track is reached. The half-life of salicylate therefore relies on the principal metabolism process used at a specific dose and is extended with rising dose. Salicylate should be used at the edge of the dosing spectrum in non-linear kinetics. Studies showed that the comparative input of the various salicylate metabolic processes is highly inter-subject variability. Unchanged salicylate urinary excretion constitutes 10% of the complete salicylate elimination. total salicylate excretion is the result of glomerular filtration, effective proximal tubular secretion via transport of organic acid and reactive cellular reabsorption. excretion of salicylates through urine is significantly pH-dependent, so as urinary pH increases from 5-8, the quantity of remaining ionized salicylates excretion is increased by up to 80% (by ionizing in saliva), from 3% of the complete salicylate intake. Glucuronide conjugation at that point winds up essential and the medication is conjugated with glutathione. With significantly higher dosages the glucuronide framework ends up saturated. A more prominent extent of the medication excreted in the urine as salicylic acid. The rate of elimination at that point relies upon urinary pH. Administration of sodium bicarbonate expands the alkalinity of the tubular filtrate subsequently acidic medications, for instance aspirin and barbiturates eliminate ionized and can't diffuse once more from the tubules to the plasma. Thus, their rate of excretion is expanded. This might be valuable in case of an overdose [26].

6. Major therapeutic applications of aspirin:

6.1 Anti-inflammatory, antipyretic, and analgesic uses:

The salicylic acid subordinates are utilized for treating pain related to gout, rheumatic fever, osteoarthritis, and RA. Aspirin, is frequently the primary medication of analgesia for mild to moderate pain in adults. In higher dosages, aspirin has anti-inflammatory action and has a work in the treatment of persistent inflammatory ailment (Commonly treated conditions like migraine, arthralgia, and myalgia). At high portions (aspirin 1g), it is anti-inflammatory originating from the restraint of cyclooxygenase and proinflammatory flagging pathways including NF- κ B [29]. In different investigations, it was inferred that Acetyl Salicylic Acid and salicylates are equally potent for anti-inflammatory specialists, yet aspirin is somewhere in the range of twenty times more powerful in comparison to salicylates in restraining an *in-vitro* enzymatic formulation

prepared from lungs of guinea pig [30]. Moreover, this is accounted that orally taken Acetyl Salicylic Acid (10 mg/kg) repressed thromboxane (TX) generation through rodent blood cells however twenty folds portion of the salicylates had negligible impact [31]. These discoveries prompted theory that the anti-inflammatory action of these medications was not identified with restraint of prostaglandin (PG) blend [32]. Gerald et al, examined the similar pharmacological activity of Acetyl Salicylic Acid and salicylates with connection toward hindrance of arachidonate cyclooxygenase and anti-inflammatory effect. They reason that Acetyl Salicylic Acid and salicylates are equally potent as anti-inflammatory operators, salicylate is less dynamic than aspirin in hindering prostaglandin generation in vitro. Aspirin is quickly metabolized, bringing about highpoint concentration of salicylate in the plasma and exudate that surpassed high point concentration of Acetyl Salicylic Acid by 30-to 50-crease. Moreover, concentration of Acetyl Salicylic Acid quickly decreased, though higher concentration of salicylate continued within serum leading to presence of their traces for 6 hr even with a single dose of Acetyl Salicylic Acid. In comparison to salicylates aspirin was significantly more powerful in hindering thromboxane B2 generation in coagulating blood [27].

6.2 Cardiovascular applications:

Aspirin lessens platelet aggregation by repressing the enzyme cyclo-oxygenase, which is fundamental for the arrangement of thromboxane A2. Its utilization is prescribed prophylactically in patients with coronary illness, for example, angina and arrhythmia just as those with past thrombotic disease [33]. Low portions are utilized prophylactically to 1) decrease the danger of repeating transient ischemic attacks (TIAs) and stroke in the individuals who have had single or various scenes of TIA or stroke; 2) lessen the danger of death in those having an intense myocardial infraction; 3) lessen the danger of repetitive nonfatal myocardial localized necrosis and additionally passing in patients with past myocardial localized necrosis or temperamental angina pectoris; 4) decrease the danger of myocardial localized necrosis and sudden demise in patients having stable angina pectoris; 5) decrease in cardiac vulnerability in patients experiencing some revascularization approach. Restraint of Cyclooxygenase-2-subordinate PG's happens to a lot higher oral Acetyl Salicylic Acid dosages in comparison to those utilized in prophylaxis of cardiovascular diseases. The proportion of IC50 values (the amount creating half enzymatic inhibition) for hindrance of COX-2/COX-1 is 166 [29]. Therefore, the antiplatelet and vasodilatory impacts of the COX-2-intervened metabolite, prostaglandin I2 (PGI2), ought to be lowest influenced at lower dosages of acetylsalicylic acid. Nagelschmitz et al, examined Pharmacological action of aspirin on i.v and orally administered by volunteers. The pharmacological action of unit doses of aspirin taken i.v (250 or 500 mg) or orally (100, 300, or 500 mg) was checked randomly, placebo controlled, hybrid investigation. Within 5 minutes, for blocking platelets coagulation was accomplished by both i.v ASA portions, mirroring fast blockage which wasn't seen with oral doses. At 5 minutes after administration, the mean decrease in arachidonic acid actuated thromboxane B2 synthesis ex vivo was 99.3% with ASA 250 mg intravenously and 99.7% with ASA 500 mg intravenously. This examination exhibits that i.v acetylsalicylic acid gives fast or reliable platelet aggregation in comparison to oral acetylsalicylic acid inside the 1st hour of

dose. Concentrates in animals have likewise appeared biochemical selectivity isn't obvious with i.v aspirin. Both i.v and orally administration of acetylsalicylic acid 5 mg/kg to rats brought about equivalent restraint of portal vein 6-keto-PGF1 α and thromboxane B2, however arrangement of inferior vena cava 6-keto-PGF1 α was spared. In people, administration of i.v or oral acetylsalicylic acid 1 g exhibit the totally suppress serum thromboxane B2, yet urinary thromboxane B2 and 6-keto-PGF1 α were likewise oppressed by intravenous ASA. Orally taken acetylsalicylic acid is a renal-sparing medication contrasted than other NSAID [30]. Gerald et al, reason that Aspirin is progressively intense in hindering platelet work after oral organization than it is as an anti-inflammatory drug. Aspirin directly affects platelet cyclooxygenase in the presystemic flow however is quickly changed over to salicylate, which, in spite of the fact that a more fragile cyclooxygenase inhibitor, achieves adequately high concentration in the peripheral area to have an impact [27]. Antiplatelet treatments with aspirin and clopidogrel have been broadly used to counteract thromboembolic occasions in chosen patients with coronary atherosclerosis [34]. It is commonly acknowledged that the primary component of this effect happens through restraint of platelet enactment and accumulation. A few studies have proposed individual fluctuation in the reactions to aspirin and clopidogrel, as surveyed with ex vivo platelet work measures [35,36]. A low level of restraint in the platelets of patients treated with these medications has been named "resistant" to aspirin or clopidogrel and has been embroiled in adverse cardiovascular results, especially after percutaneous coronary interventions [37]. The components for this study are vague, and strategies to recognize and treat it are as yet being explained. In another investigation, assessing the connection between reticulated platelets (RPs), platelet size, and platelet work in patients with stable coronary artery diseases (CAD) taking aspirin and clopidogrel. The study presume that extent of circling RPs firmly associates with reaction to antiplatelet treatment in patients with stable CAD. Larger platelets display expanded reactivity regardless of double antiplatelet treatment, contrasted with littler platelets [38]. Celestini et al, considered the combination of vitamin E with aspirin to anticipate thrombotic vascular accidents. They examined the limit of vitamin E (50 and 100 μ M) to upgrade the antiplatelet impact of aspirin. Study show that vitamin E can potentiate the antiplatelet action of aspirin by repressing the early occasions of platelet actuation pathways prompted by collagen. This finding gives a justification to joining aspirin and vitamin E to avoid thrombotic difficulties in atherosclerotic patients [27]. Coagulation disorder, paleness and hyperlipidaemia are moderately normal, especially in more established patients. Anticoagulant treatment, primarily warfarin, and platelet inhibitors, for example, aspirin, are utilized prophylactically to avert thromboembolic diseases while fibrinolytic medications can be utilized to demolish thrombi effectively shaped and can be lifesaving after a myocardial infraction or stroke.

6.3 As anticancer agent:

Later various investigations proposed advantage of acetylsalicylic acid for cancerous patients that propelled expanding endeavours to exhibit the antitumor capacity of acetylsalicylic acid and uncover the mechanism behind. Albeit dubious, gathering proof focuses to cardioprotective portions of aspirin and different NSAIDs being chemo-preventive

against colorectal malignant growth and perhaps different tumors of the stomach, throat, breast, ovary, and lung [39]. Be that as it may, large scale studies are important to survey whether aspirin can avert malignant growths concentrating on dose, age at which to start treatment, and term of treatment with randomized clinical preliminaries being basic to absolutely set up aspirin's viability and security. In addition, it is hazy what molecular and biochemical pathways are focused by NSAIDs in a general endeavour to distinguish the components by which this class of medications may restrain carcinogenesis. Thusly, disease improvement and development are progressively accepted to be driven by inflammatory cells, which animate the development and survival of malignant cells [40]. In another study, contemplated Inhibitory activity of Aspirin on Cancer Metastasis and Angiogenesis by means of Targeting Heparanase was studied. This examination distinguished heparanase, an oncogenic extracellular lattice enzyme engaged with malignant growth metastasis and angiogenesis, as a potential focus of aspirin. They found that aspirin specifically ties to Glu225 area of heparanase and represses the enzymatic action. Aspirin obstructed tumor metastasis, angiogenesis, and development in heparanase-dependent way [41]. Given that NSAIDs when all is said in done and now aspirin low hinder intense aggravation, it is enticing to theorize that maybe one of the anticancer properties of aspirin may just be the hindrance of inflammation that causes disease. All things considered, the anticancer activity and related systems of aspirin remain to a great extent obscure.

6.4 Minor or under clinical trial applications:

Aspirin as long known medication for treating inflammation is currently gaining the status of wonder medicine as it is not only beneficial in inflammatory treatments, but also treat other clinical conditions as follows:

6.4.1. External applications:

Salicylates and their congeners are widely used to treat topical ailments such as calluses, corns and warts. In the semisolid formulations like liniments, methyl salicylates are utilized as topical counter irritants.

6.4.2. Alzheimer's Disease treatment: Many clinical studies outcomes exhibited the use of aspirin and other NSAIDs in treatment of arthritis also decline the chances related to occurrence of AD. In case of NSAIDs, Indomethacin and ibuprofen shows positive results. Other NSAIDs like aspirin and other steroids used in inflammatory action like prednisolone also shows same positive feedback. Recent studies suggest the mechanism of action for NSAIDs was found to be reducing A β 42 formation via inhibition of γ -secretase, which is an action unrelated to reduction in COX. It is a curious area to study that which compound inhibit γ -secretase selectively without reducing COX generation leading to side effects causes by NSAIDs therapy. But unfortunately, none of the NSAID shows a remarkable result to overcome the progression of AD [42].

6.4.3 Radiation-induced diarrhoea.

6.5 Unwanted effects:

There are numerous systemic and local toxicity effects are produced by aspirin and other NSAIDs which are outlined

above. But there are some specific side effects which are related to aspirin and other NSAIDs. Unwanted effects, many of them occurred due to blocking of cyclo-oxygenase (COX)-1 enzyme, which mainly occurred in geriatric patients. These unwanted effects mainly include followings.

Dyspepsia, nausea and vomiting: Due to inhibition of gastroprotective prostaglandins, leads to cause of gastric damage and increased chances of haemorrhage [43].

Prolonged bleeding time: TXA₂ platelet concentration decreases via irreversible acetylation of cyclooxygenase, which suppresses platelet coagulation leading to exacerbation of bleeding time. Acetyl salicylic acid must therefore not be used for one week before an operation [44].

Metabolic processes: when aspirin or salicylates are used in higher dose, it leads to uncoupling of oxidative phosphorylation causing dissipation of heat required to produce ATPs production. This condition leads to hyperthermia due to overdosing of salicylates [43].

Skin reactions: Mechanism unknown.

Reversible kidney dysfunction: In patients with compromised or kidney dysfunction leads to inhibition of PG E₂-mediated vasodilatation [43].

Nephropathy associated with Analgesics-: This condition occurred due to higher amounts of NSAIDs (e.g. paracetamol) for quite longer duration and generally it is irreversible [43].

Disorder related to Liver and bone marrow depression: Relatively uncommon.

Bronchospasm: Seen in 'aspirin-sensitive' asthmatics.

Reye's syndrome: an uncommon disease of youngsters which is portrayed by liver encephalopathy causing an intense viral disease and mortality rate is generally high [43].

Salicylate poisoning is a consequence of disturbance of the acid-base and the electrolyte balance that might be found in patients treated with high dose of salicylate-containing drugs and in attempted suicides. These medications can uncouple oxidative phosphorylation (for the most part in skeletal muscle), prompting expanded oxygen utilization and in this way expanded formation of carbon dioxide. This animates breath, which is likewise invigorated by an immediate activity of the medications on the respiratory centre. The subsequent hyperventilation leads to alkalosis of respiratory system which is regularly repaid by renal components including expanded bicarbonate discharge. Since it is cover up on a decrease in plasma bicarbonate, an uncompensated respiratory acidosis will happen. This might be entangled by a metabolic acidosis, which results from the aggregation of metabolites of pyruvic, lactic and acetic acids. In the CNS, initial stimulation with excitement followed by unconsciousness and respiratory depression. Unsettling influences of haemostasis can likewise happen, for the most part because of reduced platelet accumulation. Salicylate poisoning is a medical emergency. The acid- base imbalance influence found in kids is generally a metabolic acidosis, while that in grown-ups is a respiratory

alkalosis [43,44].

7. Effects of aspirin on major body systems:

7.1 Central Nervous System:

Their analgesic impact of Aspirin-like drugs is classically attributed within the pain-processing site to a peripheral site of action. However, there is compelling proof that these agents provide a key element to the general analgesia. Experimental and clinical studies are evaluated here referring to this difficult proposition. Supraspinal mechanisms are probable to play a significant role. Some studies promote monoaminergic control systems participation. Other information show that by inhibiting cyclo-oxygenase activity, these drugs behave centrally. The interactions between prostaglandins and different neurotransmitters indicate that it is possible to link both processes [45]. The EEG impacts of aspirin were researched in ordinary adult males at single doses of 0.65 and 1.95 gm. The quantitative EEG, self-reporting symptoms, and cognitive functions were impacted by 1.95 gm compared to placebo. Similar in direction and pattern were the impacts of 0.65 gm, but measurable importance failed. Aspirin's EEG profile is different from other psychoactive substances. During routine clinical use, its interaction with sedative drugs should be regarded [46].

7.2 Respiratory system:

The patients suffering from Aspirin-exacerbated respiratory illness (AERD) are generally more susceptible to aspirin, in which use of aspirin leading to asthma, rhinosinusitis and sensitivity to aspirin. Highly selective COX-2 inhibitors are not cross-sensitive. AERD's diagnosis is produced through provocative testing of challenges. Patients may be desensitized to aspirin and NSAIDs following a favourable aspirin challenge. With ongoing daily administration, the desensitized state can be retained forever. There is a refractory period of about 48 hours after desensitization to adverse effects from aspirin. AERD's pathogenesis continues unknown. Patients may also use weak inhibitors of COX-1 such as salicylate sodium or trisalicylate choline magnesium. In comparison with non-AERD patients, treatment of AERD patients with antileukotriene medicines was useful but not preferential. Aspirin desensitization is an option therapy for many AERD patients. This is especially efficient in decreasing congestion of the upper airway mucosa, nasal polyps and systemic steroids [47].

7.3 GIT:

The systemic and topical use of aspirin is associated with GIT complications like bleeding in stomach mucosa and peptic ulceration, which have shown more susceptibility in patients with age, male sex, ulcer history and concurrent medication. Sometimes the GIT side effects of aspirin overpower the beneficial cardiovascular (CVS) effects in patients having a tendency of hyperacidity. At the same time, cessation of aspirin therapy in such patients reverts the beneficial CVS effects. Although researches have proved that use of some antisecretory agents along with aspirin like PPI's can benefit in adverse GIT effects without compromising with beneficial CVS effects [48].

7.4 Excretory system:

Salicylic acid is mainly excreted through renal pathway in the form of salicylic acid (75 percent), free salicylic acid (10 percent), salicylic phenol (10 percent) and acyl (5 percent) glucuronides, and gentisic acid (< 1 percent). In small doses, the excretion of aspirin follows first order kinetic i.e the excretion rate is directly proportional to salicylic acid present and the half-life of salicylic acid decreased (2-3 h), however with increased dose, the excretion rate become independent of its concentration and approaches zero order elimination rate and with this, its half-life increased up to 15-30 h. Urine pH have a major impact on the rate of excretion. Salicylate excretion rises fourfold when urine pH is > 8.0. Due to acidic nature, the drug is highly ionized at this pH and cannot easily spread from the tubular fluid. The positive impacts of angiotensin-converting enzyme (ACE) inhibitors are countered by high doses of aspirin. It is not known how low-dose aspirin impacts renal function with concomitant ACE-inhibitor therapy [49]. The patients having CVS disorders, both aspirin and ACE inhibitors have positive impacts on prognosis. They are normally prescribed together for this purpose. It is believed that some of the positive impacts of ACE inhibitors are due to decreased bradykinin degradation. Bradykinin enhances prostaglandins with nitric oxide and vasodilating [50].

8. Drug interactions with aspirin:

Simultaneous intake of Acetyl Salicylic Acid along with different medicines may deliver adverse effects. Since Acetyl Salicylic Acid is most frequently prescribed drug, so patients should be aware to read and understand the labels, so they can understand the dose, its dosing frequency etc to avoid overdosing [39]. Acetyl Salicylic Acid bound to proteins up to 90 percent protein bound and can be uprooted from its protein-restricting destinations, bringing about expanded concentration of free salicylate; on the other hand, aspirin could displace other extremely protein-bound medications, for example, warfarin, bringing about higher free concentration of the other individuals. Aspirin causes a possibly risky increment in the impact of warfarin, halfway by dislodging it from plasma proteins and mostly in light of the fact that its impact on platelets. Acetyl Salicylic Acid additionally interact with uricosuric drugs, and in light of the fact that low portions of aspirin may, all alone, decrease urate discharge, aspirin ought not to be utilized in gout. Simultaneous utilization of ketorolac and aspirin is contraindicated in view of expanded danger of GI bleeding and platelet accumulation hindrance. Children who have gotten live varicella infection immunization ought to keep away from aspirin for no less than about a month and a half after inoculation to avoid Reye's disorder [44].

8.1 Other Unwanted Effects

Other, substantially less normal, undesirable impacts of NSAIDs incorporate cerebral effects, depression of bone marrow and hepatic issue and this worsen in case of renal dysfunction. Roughly, around 5% of patients taking NSAIDs may encounter Acetyl Salicylic Acid subtle asthma. The correct component is obscure; however, hindrance of COX is ensnared. Near about all NSAIDs avoid platelet conglomeration and subsequently may draw out bleeding. Once more, aspirin is the principle issue in such manner [44].

9. Pharmaceutical research work performed on aspirin and future prospective:

Aspirin is poorly dissolvable in water and causes gastrointestinal (GI) disturbance. Orally administered aspirin requires high and successive dosing in light of the fact that it experiences broad presystemic metabolism. Likewise, long term and chronic oral aspirin is related with genuine gastrointestinal symptoms. Along these lines, if the dissolvability and bioavailability of aspirin can be increased, it will decrease the gastrointestinal reactions [44]. There are various attempts made by researchers to beat this issue by planning chewable tablets, orally dispersible tablets, foaming tablets, film covered tablets and capsules and so on. Different strategies incorporate solid dispersion approach, complex development, cocrystallization and so on yet results are as yet not palatable or efficient. Chaudhari, et al, prepared Solid Dispersion of aspirin by Physical Mixture and Fusion (Melt) Method utilizing Aspirin and Polyethylene Glycol 6000 as carrier in the proportion of 1:1, 1:2, 1:3 and 1:4. The complex of Aspirin with Polyethylene Glycol 6000 shows upgraded dissolvability than the unadulterated medication and the complex can likewise lessen the gastrointestinal disturbance. In solid dispersion approach, the medication is scattered in very fine state in a latent water-solvent transporter in the solid state [1]. Various openly water-dissolvable materials, for example, citrus extract, bile acids, sterols and related mixes and polymers like Polyvinylpyrrolidone and Polyethylene Glycols were utilized as carrier for solid dispersion approach. By this methodology, the disintegration rate and bioavailability of inadequately dissolvable medication can be expanded. While in another investigation Haeria, et al, prepared aspirin and nicotinamide cocrystals in equimolar proportion (1:2) through solvent drop grinding technique. The study presume that crystallization demonstrates solubility improvement essentially than standard aspirin drug. In crystallization process, the intermolecular bonding within drugs and cofomers can tailor the physical, chemical and pharmaceutical characteristics of drug without altering its therapeutic effect [44]. Cheney et al, arranged cocrystal of meloxicam and aspirin. The cocrystal of meloxicam and aspirin showed predominant kinetic solubility and had the possibility to fundamentally reduce the time required to achieve the human therapeutic concentration compared with parent drug, meloxicam [51]. Shekh et al, arranged aspirin- β - cyclodextrin inclusion complexes to improvise its dissolution profile. *In vitro* drug release showed an improved disintegration rate of Aspirin [52]. These newer methods including nanotechnology, solid dispersion approach, complex formation, crystallization etc. have bright future in pharmaceutical scenario for improvising the dissolution rate and bioavailability of poorly water-soluble drugs. Generally speaking, these investigations require further developed research concerning different strategies to improve aspirin solubility.

10. Conclusion:

Most of the drugs which were discovered in late 80's century has been substituted by newly discovered drugs and therefor are not used presently. However, aspirin is amongst the drugs discovered in late 80's century, which has retained its clinical importance till date to an extent that it is the first line drug of choice in many diseases like inflammation, antipyretic, analgesic, antiplatelets etc. The ongoing researches on this molecule have added to its importance now a days, aspirin is

not only used as anti-inflammatory or analgesic drug but its dose dependent effects on CVS and platelets etc have attracted the scientists for exploitation of this molecule as a potential anti-thrombolytic and anticancer agent. And this is not an end, the ongoing researches have shown hope that this molecule could be used as anticancer agent in future.

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Conflict of Interest

The authors do not have any conflict of interest.

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