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Review Article

## Pharmacology, Pharmaceutics and Clinical Use of Aspirin: A Narrative Review

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### ABSTRACT

**Background:** Aspirin is one of the most frequently used and cheapest drugs in medicine. Since its first synthesis in 1897, several medicinal roles and mechanisms of action of Aspirin have become apparent, the latest among these being its role in cancer prevention and treatment.

**Objective:** We present a review of Aspirin's biochemistry and pharmacology, as well as the clinical use of Aspirin. The communiqué also suggests possible strategies for maximizing the gain of Aspirin as a wonder-drug of the future.

**Methods:** The literature search strategy covered printed and online sources, including manual library search (PubMed), Embase, Medline, and Cochrane Library. For papers written in English and published in the last ten years. A systematic analysis of available data was subsequently performed based on the review questions. An estimated 155 articles were found online, and twenty-eight articles utilized in the final analysis.

**Discussion:** Aspirin belongs to the non-steroidal anti-inflammatory drugs with a wide range of pharmacological activities, including analgesic, antipyretic, and antiplatelet properties. Discovery of antiplatelet effects led to the increasing use of Aspirin as an anti-thrombotic agent in the prevention of cardiovascular diseases from the 1980s, and firm evidence supporting its usefulness has continued to accumulate. Aspirin irreversibly inhibits platelet function by acetylating cyclooxygenase (COX), which is involved in the production of a potent platelet stimulator, thromboxane A<sub>2</sub>. The inhibition of COX-2 by Aspirin forms the basis of its anticipated role in preventing colorectal cancer and Alzheimer's disease and the inhibition of the progression of these diseases. It has been pointed out that the incidence of cardiovascular events tends to be high among patients who are Aspirin resistant, but the reason for this increased incidence remains unclear.

**Conclusion:** The emerging future interest is to accrue evidence in favor of Aspirin as the novel therapeutic drug for combating severe acute inflammation and thrombosis associated with the cytokine storm in COVID-19 patients. Notably, a randomized clinical trial, to test a range of potential treatments for COVID-19, includes low-dose Aspirin as anti-inflammatory and antiplatelet treatment.

**Keywords:** Aspirin; Anti-platelet; Nonsteroidal Anti-inflammatory Drug; Pharmaceutical; Pharmacodynamic; Pharmacokinetic.

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### 1.0 BACKGROUND

Bayer AG synthesized aspirin or medicinal acetylsalicylic acid in 1897 obtained from barks of willow tree [1-3]. Apart from analgesic, antipyretic and anti-inflammatory properties, several other therapeutic roles of Aspirin have become

apparent since then. These include its use as an anti-thrombotic agent in the prevention of cardiovascular diseases (CVD) due to antiplatelet effects [1, 4] and, more recently, as an agent for cancer prevention and treatment. Cancer and CVD comprise a substantial proportion of the global disease burden and are the leading causes of disability

and death in the developed world [1, 7]. Aspirin has considerable potential to reduce these if used prophylactically in the general population. However, Aspirin is also associated with excess bleeding, particularly gastrointestinal (G.I.) bleeding and hemorrhagic stroke being the most significant concerns. Evaluation of Aspirin as a prophylactic measure for the general population requires a careful assessment of both benefits and harms. It is essential to recognize that although relatively common, the vast majority of Aspirin related adverse effects (excluding intracranial bleeding) does not have long-term sequelae and are rarely fatal, especially for individuals under the age of 70 years [1, 8].

Interestingly, inflammation is a defensive response of an organism against invasion by foreign bodies like bacteria, parasites, and viruses. An acute inflammatory response is manifested as redness, heat, swelling, pain, and the loss of function. Increased vascular permeability, accelerated blood flow, and nerve fiber sensitization is associated with swelling, redness, and pain, respectively [9, 10]. The protective effects of the inflammatory cascade and the potential for tissue destruction are usually balanced in a healthy state. On the other hand, chronic inflammation is usually characterized by substantial damage and recovery of injured tissues from an inflammatory response [9, 11].

Finding a safe and effective drug to control inflammation has been a challenge. Management of inflammatory diseases either with steroidal or non-steroidal drugs is a traditional clinical practice. The non-steroidal anti-inflammatory drugs (NSAIDs) inhibit early steps in the biosynthesis of prostaglandins through the inhibition of cyclooxygenase (COX). The NSAIDs are essential drugs used to reduce untoward consequences of inflammation [9, 12-14]. The current emerging interest is to conduct further study to provide evidence for Aspirin as the novel therapeutic drug for combating severe acute inflammation and thrombosis associated with the cytokine storm in COVID-19 patients.

## 2 OBJECTIVES OF THE STUDY

We present a review of Aspirin's biochemistry and pharmacology, as well as clinical use of Aspirin. The communiqué also suggests possible strategies for maximizing the gain of Aspirin as a wonder-drug of the future.

## 3.0 METHODS

### 3.1 Literature Search Strategy

We identified relevant articles to date using a manual library search (PubMed), Embase Medline, and Cochrane Library as well as ClinicalTrials.gov for current trials on hand hygiene practices amid COVID-19 pandemic in sub-Saharan Africa. The Google search was done covering the following periods between March 1 and July 30, 2020, for papers written in English and published in the last ten years. Interestingly, the search was conducted

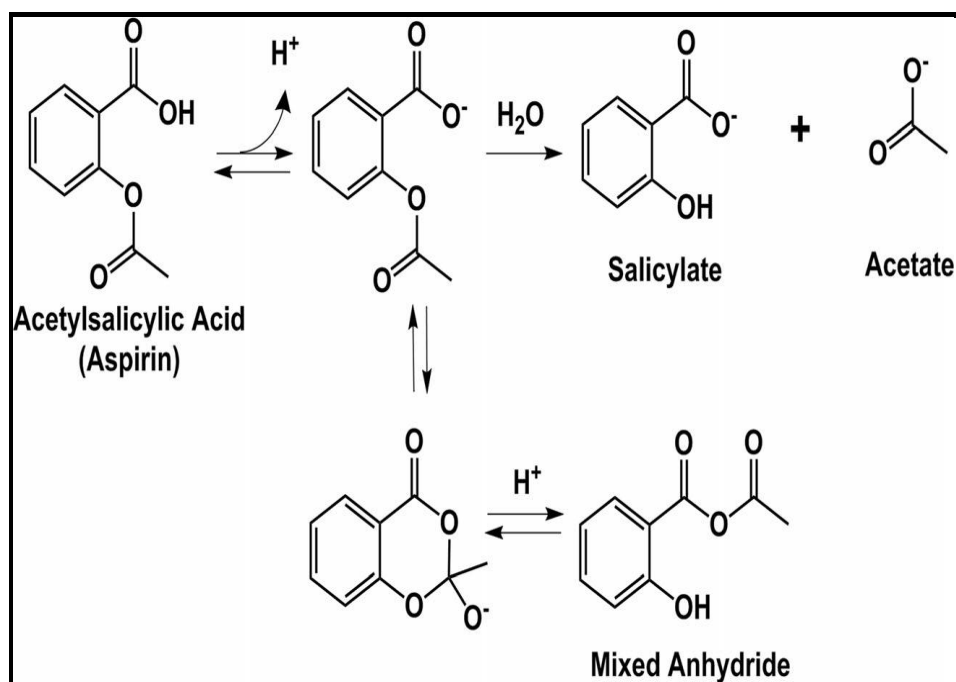
using different keywords, which were combined during the literature search and where applicable. The final search terms include these categories: "Aspirin" or "Acetylsalicylate" or "Acetylsalicylic acid." Others are "non-steroidal anti-inflammatory drugs" "NSAIDs." Moreover, there were attendant nine million hits at the initial period, after that, the search was narrowed to Aspirin and Acetylsalicylic acid research themes and relevant references were collected, analyzed, producing the subsequent 155 articles. Consequentially, the study team read through them, and a final selection of the most pertinent twenty-eight research articles was then critically reviewed in the final analysis.

### 3.2 Data Analysis

The data were extracted according to the review questions, and a narrative synthesis was conducted to identify the pharmacology, pharmacodynamics, pharmaceuticals; besides, the ever emerging role as well as clinical use of Aspirin.

## 4.0 THE BIOCHEMISTRY AND PHARMACOLOGY OF ASPIRIN

"Aspirin is an O-acetyl derivative of salicylic acid (ASA—acetylsalicylic acid), and its dominant mechanism of action is believed to be through the transfer of this acetyl group to (-OH) and amino (-NH<sub>2</sub>) functionalities present in biological macromolecules. The acyl ester group is also unstable under primary conditions, and its hydrolysis to acetate is believed to proceed by a general base-assisted mechanism as described previously" [15-17]. "More recent computational studies have suggested an n→π\* interaction between the aromatic carboxylic acid and the acetate group" [15, 18]. "This interaction is consistent with a nuclear magnetic resonance spectroscopy (NMR) study positing a cyclic hemioorthoester under primary conditions that can rearrange to give either the parent aspirin anion or a mixed anhydride as seen in **Figure 1**" [15, 19]. Although the prevalence and role of the mixed anhydride in Aspirin's biochemistry have yet to be determined, the broad scope of anhydride reactivity may help explain the promiscuous acetylation activity of Aspirin in biological systems [15, 20, 21]. Interestingly, "it has also been shown that the mixed anhydride can react with the primary amino group of glycine in organic solvents to form N-salicyloylglycine, suggesting a second class of aspirin-mediated protein modifications" [15, 22]. With co-workers, Richard Farr demonstrated the non-selectivity of aspirin-mediated acetylation in 1968 [15, 23]. "In these experiments, Aspirin labeled with <sup>14</sup>C at the acetyl carbonyl carbon was incubated with a series of blood proteins as well as common enzymes and nucleic acids. Following dialysis, substantial radiolabeling of albumin, immunoglobulins, α-macroglobulin, and other enzymes was observed. More recent mass spectrometry-based studies have validated this initial finding. The list of proteins acetylated by Aspirin has grown to include histones, IKKβ (I-kappa-β-kinase beta) many others," [15, 24-26].



Figures 1: The chemistry of Aspirin under basic conditions [15, 19]

*Deprotonation of the carboxylic acid results in the formation of the aspirin anion which abstracts a proton from water to generate a nucleophilic hydroxide anion. Recent work also suggests that a mixed anhydride can be formed under basic conditions through a hemioorthoester anion intermediate.*

“At high concentrations (micromolar to millimolar), Aspirin has been shown to react with nucleophilic groups on proteins resulting in irreversible acetylation. These include the functional groups of the residues lysine (-NH<sub>2</sub>), arginine (-NH<sub>2</sub>), serine (-OH), threonine (-OH), tyrosine (-OH), and cysteine (-SH). The synthesis of Aspirin is highly straightforward. Aspirin can be synthesized under acidic or basic conditions using acetyl chloride or acetic anhydride in the presence of salicylic acid” [15, 27, 28]. Synthesis of 13C- or 14C-labeled Aspirin has also facilitated the real-time analysis of acetylation of ubiquitin [15, 29], hemoglobin [15, 30], and human serum albumin [15, 27].

## 5.0 PHARMACOKINETICS AND PHARMACODYNAMICS OF ASPIRIN

“Inhibition of COX-1 and COX-2 activity by aspirin is attributed to the covalent modification of active site serine residues (Ser 530 in COX-1 and Ser 516 in COX-2)” [15, 31, 32]. “The acetylation of these side-chain hydroxyl groups results in irreversible inhibition through the active site's steric blockage. This effect can be recapitulated by acetic anhydride, which acetylates nucleophilic groups, albeit at a much higher rate than Aspirin,” [15, 24, 33]. While site-selective acetylation of COX-1 and COX-2 is thought to be driven in part through molecular recognition of Aspirin's benzoic acid functionality, the ‘non-specific’ acetylation activity of Aspirin is thought to be driven largely by the chemical environment [15, 34]. “For example, in the highly acidic environment of the gastric mucosa (pH = 2–3), the carboxylic acid (pK<sub>a</sub> = 3.5) exists mainly in the protonated state, which is predicted to reduce the rate of hydrolysis. In contrast, the alkaline environment found in the gastroduodenum (pH = 8.0) results in deprotonation of the carboxylate group and an increased rate of both hydrolysis and transacetylation” [15, 34]. “In addition to environmental pH, the aromatic ring and carboxylic acid also play essential roles in Aspirin's reactivity and stability. These effects are mediated through hydrogen bonding of the carboxylic acid and the free hydroxyl, or through π – π stacking interactions

with the aromatic ring. The stabilization of the salicylic acid moiety has also been shown to be important for efficient acetylation of free nucleophilic residues on protein surfaces” [15, 31, 32]. “Aspirin is readily absorbed in the acidic environment of the gastric mucosa. At this interface, Aspirin can readily inhibit the biosynthesis of prostaglandins associated with the protection of the stomach lining” [15, 35, 36]. Absorption in the stomach lining is facilitated by the molecule's net neutral charge resulting from protonation of the carboxylic acid at low pH. As predicted by mechanistic studies, minimal, if any, Aspirin undergoes spontaneous hydrolysis at this pH. Also, at lower pH, it would be expected that the protonation of the carboxylate would prevent the intramolecular rearrangement of Aspirin to the acetylsalicylic acetic anhydride [15, 22]. “Aspirin moves from the stomach's highly acidic environment to the nearly neutral pH of the duodenum (pH 7–8), and the small intestine (pH 7.3), deprotonation of the aromatic carboxylic acid is favored resulting in a net negative charge. The half-life of Aspirin in the bloodstream was previously shown to be 13–19 min with a non-enzymatic hydrolysis rate of 0.023 min<sup>-1</sup> at 37 °C in individuals given a single oral administration of aspirin” [15, 37]. “Approximately 70% of Aspirin reaches the peripheral circulation intact with maximum serum concentrations observed at 25 min after administration. After entering the bloodstream, Aspirin undergoes enzymatic hydrolysis to yield acetate and salicylic acid. The major enzymes hydrolyzing Aspirin in plasma are believed to be cholinesterases” [15, 37], supported by the observed decrease in hydrolysis in the presence of anticholinesterase inhibitors [15, 38].

“Most recently, acetylhydrolase I, an intracellular erythrocyte platelet-activating factor, has been characterized as the major aspirin hydrolase of human blood,” [15, 39]. “In the liver, carboxylesterases are believed to carry out this role. In the bloodstream, Aspirin's platelet uptake is driven by concentration-dependent passive diffusion” [15, 40]. “In vitro studies have shown that 20% of soluble aspirin is taken up in platelets, although only 0.05% undergoes acetyl

transfer to cellular proteins as measured by SDS gel electrophoresis" [15, 41]. Intravenous Aspirin has a distribution half-life of about 3 min and inhibits prostaglandin biosynthesis within 5 min of administration, reflecting the rapid onset of inhibition compared to oral dosing [15, 42]. Enteric-coated Aspirin has been employed to decrease the bleeding effects in the gastrointestinal tract. This formulation typically increases the rate of absorption of Aspirin and delays its metabolism and activity. Another study showed that enteric-coated aspirin results in delayed onset of antiplatelet activity and a loss of aspirin bioavailability due to hydrolysis [15, 43]. "Recent studies by Lichtenberger *et al.* demonstrated that aspirin could enter the lymph fluid directly when administered intragastrically or intraduodenally, potentially increasing its pharmacologic activity as a chemopreventive agent for colorectal cancer" [15, 44].

The distribution of Aspirin is further enhanced by binding to human serum albumin [15, 45, 46]. "Human serum albumin is the most abundant protein found in blood and is often used as a plasma shuttle for steroids, hormones, and other small molecules. Binding studies suggest a conformational

change in albumin upon acetylation that can influence transport and metabolism of other critical metabolites and drugs. For example, aspirin-induced acetylation of albumin can inhibit glucose binding" [15, 47], while increasing the binding of other molecules, as observed with the increased affinity of acetylated albumin for the marker anion acetate [15, 48]. "Aspirin pharmacokinetics and pharmacodynamic are also influenced by the interaction of other metabolites and serum albumin," [15, 46]. However, "Aspirin acetylation of serum albumin likely inhibits the binding of other metabolites commonly transported by albumin. In vitro studies have shown serum albumin binding and acetylation is dependent upon fatty acid-binding," [15, 49], pH [15, 50], and temperature [15, 51]. Salicylic acid is metabolized majorly by glucuronidation by several UDP-glucuronosyltransferases (especially UGT1A6). Subsequent metabolites of Salicylic acid are cleared from circulation via the kidneys with a serum half-life of approximately two hours [15, 52] [15, 52]. A summary of the most common reactions of Aspirin in biological systems is summarized in **Figure 2**; while the biochemical metabolites of Aspirin in human is shown in **Figure 3** [15, 19].

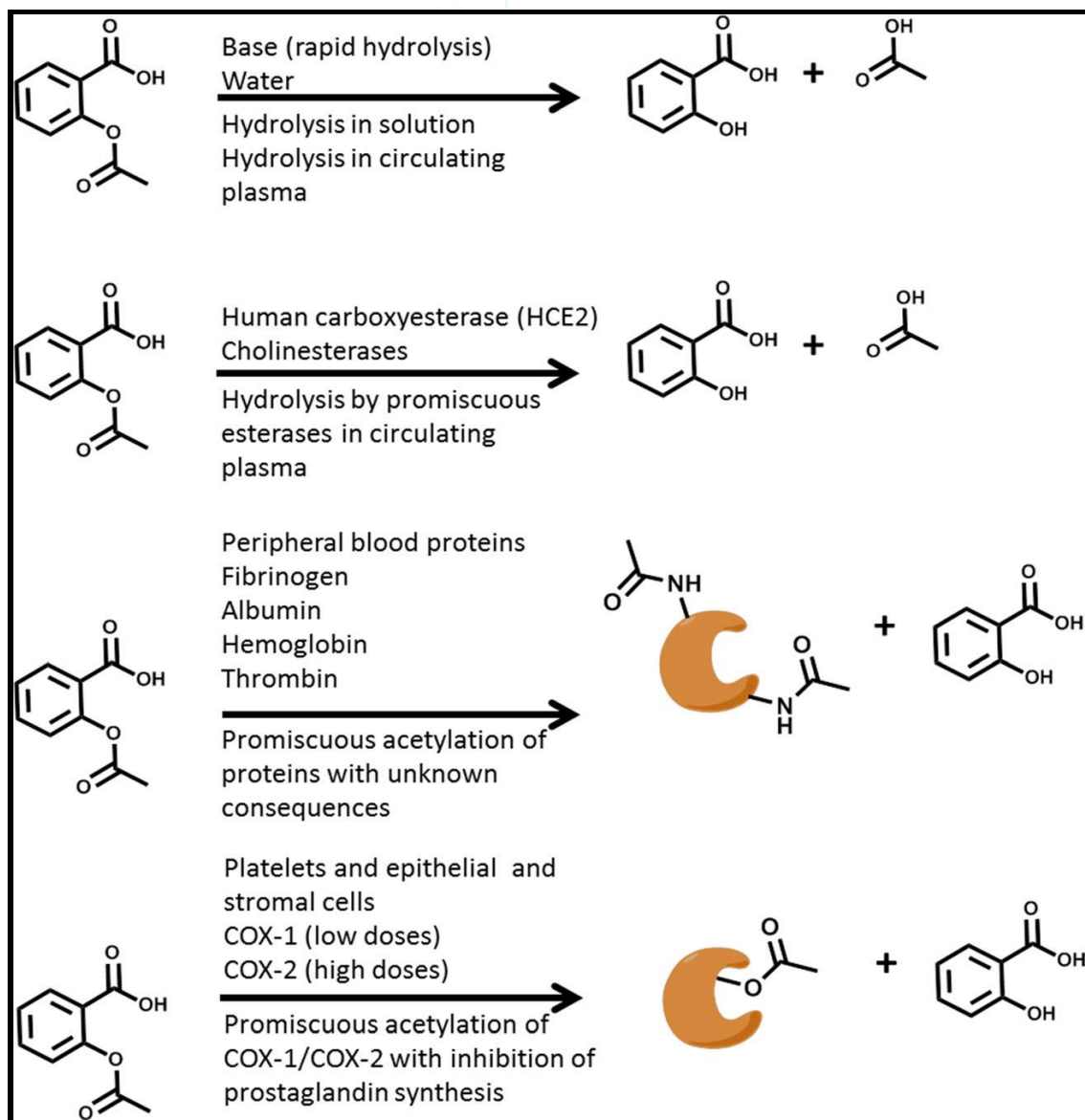


FIGURE 2: Reactivity of Aspirin in different biological environments of proteins [15, 52]

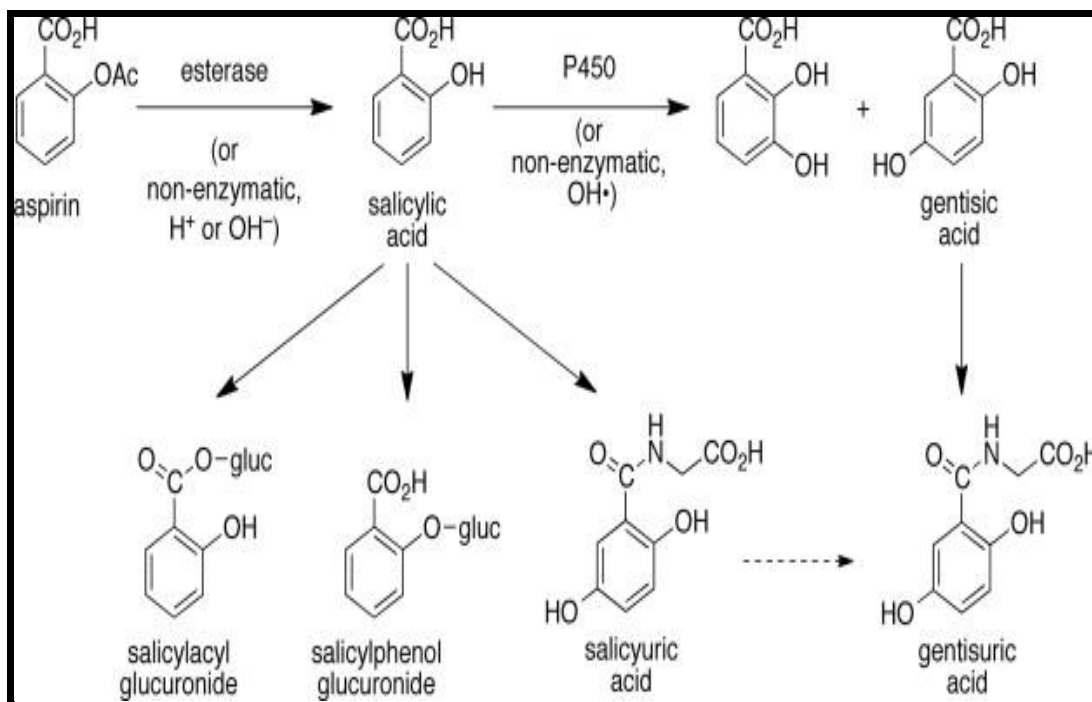


FIGURE 3: Aspirin and the biochemical metabolites in human [15, 19]

The diagram shows the chemical structure of aspirin, highlighting the salicylate group (a benzene ring with a carboxylic acid group and a hydroxyl group) and the reactive acetyl group (an ester linkage to a methyl group).

**Reactive acetyl group**

- ✧ Irreversible inactivation of platelet COX-1 by acetylation of serine-529 leading to inhibition of thromboxane-A2 production avoiding the vasoconstriction and platelet aggregation induced by this prostanoid [1].
- ✧ Acetylation of COX-2 (serine-516) inhibiting prostaglandin production but redirecting its catalytic activity, leading to the production of 15(R)-hydroxylicosatetraenoic acid as a substrate for new biologically active mediators aspirin-triggered lipoxins (ATL) [2].
- ✧ Acetylation of endothelial NO synthase (eNOS) eliciting nitric oxide release from vascular endothelium [3].
- ✧ Induction of expression and enzymatic activity of the heme oxygenase-1 (HO-1) in endothelial cells, that catabolizes heme, and contributes to the reduction of oxidative stress, injury, and inflammation [4].
- ✧ Acetylation of multiple cellular proteins such as the tumor suppressor protein p53, fibrinogen and human serum albumin, among others [5].

**Salicylate group**

- ✧ Inhibition of binding of CCAAT/enhancer-binding protein-β to its promoter region of COX-2 and of inducible nitric oxide synthase (iNOS) genes [6].
- ✧ Induction of proton transportation across cell membranes which leads to uncoupling of oxidative phosphorylation which in turn showed a decreased proliferation and cell death in tumoral cells [7].
- ✧ Prevent activation of genes involved in the pathogenesis of the inflammatory response through blocking activation by NF-κB [8].

FIGURE 4: Pharmacological and biological actions of Aspirin by its salicylate and reactive acetyl group [53-57]

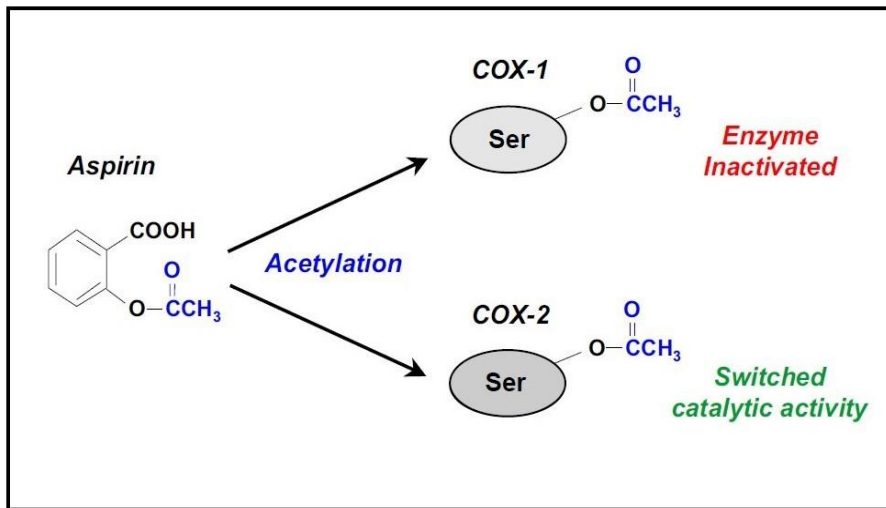


FIGURE 5: The novel mechanism of action of Aspirin [53, 58]. COX: cyclooxygenase; SER: serine

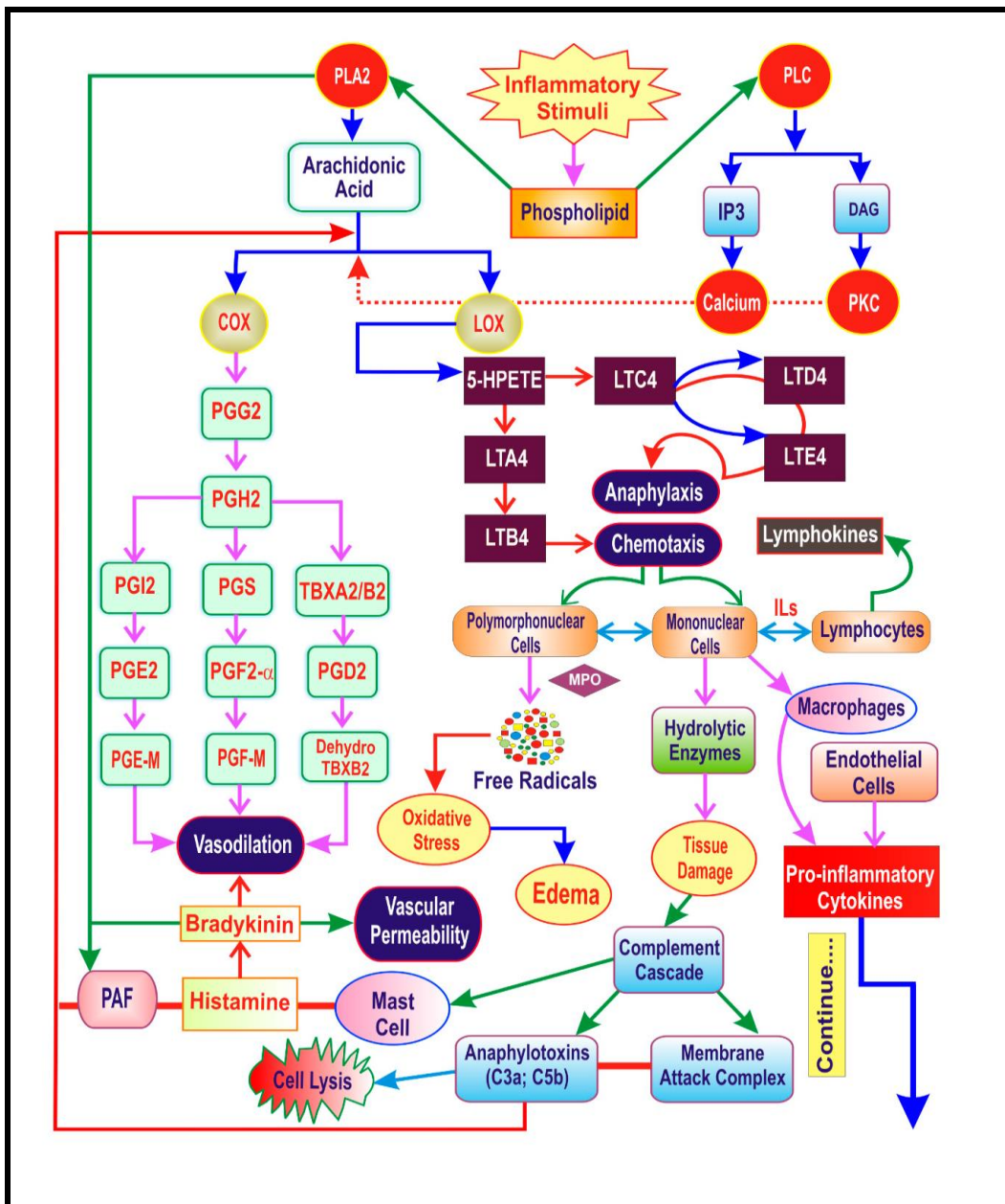
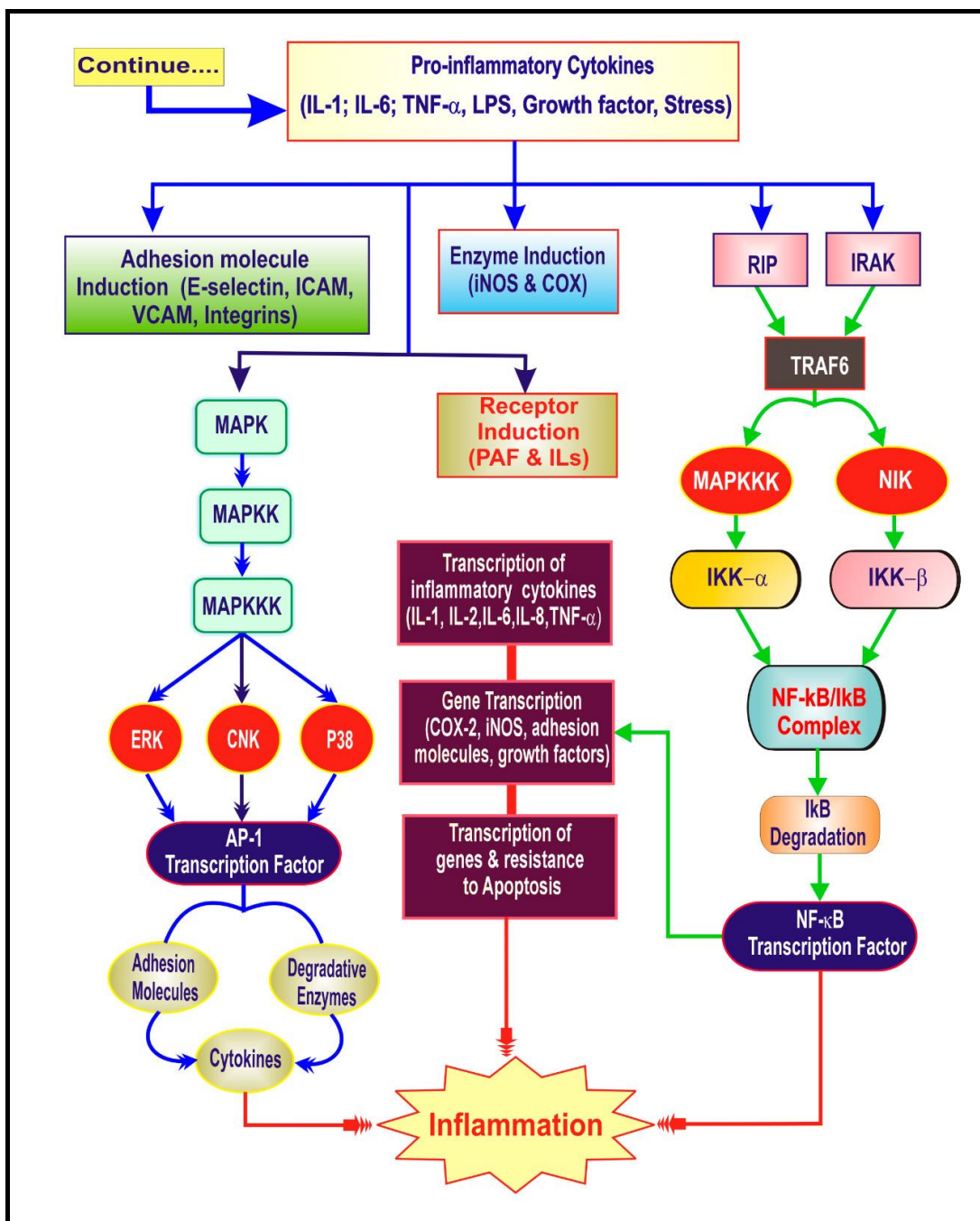


FIGURE 6: (A) Synthesis of pro-inflammatory and pro-resolving lipid mediators from Arachidonic acid (AA) [53, 58, 59]. The schematic diagram describes the inflammatory cascade; and the arrow in the figure represents process.



**FIGURE 6: (B) Synthesis of pro-inflammatory and pro-resolving lipid mediators from Arachidonic acid (AA) [53, 58, 59].** The schematic diagram describes the inflammatory cascade; and the arrow in the figure represents process.

**6.0 A NOVEL MECHANISM OF ACTION FOR ASPIRIN**

**6.1 Cyclooxygenase (COX) Pathways**

Aspirin is a widely used non-steroidal anti-inflammatory drug (NSAID). The common cyclooxygenase pathway is as highlighted in **Figure 4** [53-57]. It is well documented that "Aspirin irreversibly inhibits cyclooxygenase (COX) by acetylation of an amino acid serine residue, as seen in **Figure 5**. Also, it blocks the subsequent biosynthesis of prostaglandins and thromboxane," [53, 58]. "COX has at least two forms, COX-1 and COX-2. COX1 is the main form present in mature platelets in the blood, where it transforms arachidonic acid to the intermediates PG-G/H, which are subsequently converted to thromboxane A2. Thromboxane A2 is a vasoconstrictor and potent platelet activator. Thus, inhibition of thromboxane A2 formation explains Aspirin's anti-thrombotic properties," [53, 58]. In the early 1990s, the

second form of COX was identified, namely, COX-2. COX-2 was initially conceptualized as an "inducible" COX that is elevated in its quantity by a wide range of agents that stimulate inflammation or cell division and seems to be responsible for local formation during inflammation and cancer. The synthesis of pro-inflammatory and pro-resolving lipid mediators from arachidonic acid within the inflammatory cascade is as highlighted in **Figure 6 (A)** and **Figure 6 (B)** [53, 58, 59].

Many recent studies demonstrated that "low-dose aspirin evokes beneficial effects not only in the prevention and treatment of cardiovascular diseases, but also in decreasing the incidence of lung, colon and breast cancers, and perhaps Alzheimer's disease" [53, 58, 60]. "Although inhibition of prostaglandins and thromboxanes can account for aspirin's therapeutic benefits, aspirin's ability to regulate neutrophil-

mediated inflammation remains of interest," [53, 58, 60]. Hence, low-dose aspirin effects that go beyond the inhibition of prostaglandins and thromboxanes are becoming increasingly apparent. In this regard, Aspirin, to its well-appreciated ability to inhibit prostaglandins and thromboxanes, can also 'switch on' the production of the body's anti-inflammatory lipid mediators, namely aspirin-triggered lipoxins (ATL) [53, 58, 60]. "This novel class of mediators functions as local 'braking signals' in inflammation and actively participates in dampening host immune responses and quickly bringing the inflammatory reaction to a closure, a process called resolution. Thus, they may account at least in part for Aspirin's clinical benefits distinct from Aspirin's anti-thrombotic action," [53, 58, 60].

## 6.2 Mechanism of Platelets Action in Hemostasis

### 6.2.1 Platelet Activation and Thrombogenesis

"Upon injury of the blood vessel intima, as it occurs after trauma or rupture of an atherosclerotic plaque, subendothelial collagen and von Willebrand factor (vWF) are exposed to circulating blood components. Platelets adhere to both collagen and vWF on the injured endothelium through their glycoprotein Ia/IIa and Ib/V/IX receptors, respectively, eliciting the release of calcium," [61, 62]. "Calcium induces a conformational change in the platelet glycoprotein IIb/IIIa (gp IIb/IIIa) receptors, so they can bind circulating fibrinogen molecules. Calcium also stimulates the release of alpha-granules and dense granules. P-Selectin, one of the proteins released from alpha-granules, mediates monocytes' adhesion and neutrophils to activated platelets," [61, 63]. This function is integral to the recruitment of leukocytes into newly-formed thrombi, the perpetuation of thrombogenesis, and the overall hemostatic process [61, 63]. "Dense granules release adenosine diphosphate (ADP), which further perpetuates platelet activation by binding to ADP-specific receptors (P2Y1) and promotes the action of phospholipase A2 on membrane phospholipid compounds to produce arachidonic acid (ARA)" [61, 64]. "Arachidonic acid is subsequently converted into thromboxane A2 (TXA2) and prostaglandins (mainly G2 and H2) within platelets, a conversion mediated by thromboxane synthase and the cyclooxygenase (COX) isoenzymes 1 and 2, respectively" [61, 65]. "TXA2 is the most critical platelet activator and functions by inducing expression of fibrinogen receptors (gp IIb/IIIa) on the platelet membrane and binding to TXA2 receptors on the surface of other platelets triggering their activation" [61, 64]. It also plays a secondary, but equally important role in hemostasis, as a potent vasoconstrictor. Platelet activation also occurs with the attachment of other freely circulating nascent compounds, such as ADP, fibrinogen, thrombin, adrenalin, and prostaglandin I2, to corresponding ligand-specific receptors [61, 64].

### 6.2.2 Aspirin effect on Platelet Activation

"Aspirin irreversibly inhibits COX-1 in platelets by acetylating its serine-529 residue, thereby blocking TXA2 and other eicosanoid production from ARA. TXA2 is the most significant trigger for platelet activation. Because platelets lack a nucleus and therefore are deprived of protein synthetic ability, this inhibition cannot be overcome by new COX-1 synthesis and lasts for the platelet's lifespan (7-10 days). Aspirin-induced COX-1 inhibition is rapid, irreversible, and saturable at low doses (dose-independent)," [61, 64]. After a single 325mg dose of Aspirin, platelet COX-1 activity is completely inhibited and recovers by about 10% per day, due to nascent platelet release in the circulation [61, 64].

## 7.0 ASPIRIN ROLE IN THROMBOSIS AND CARDIOVASCULAR DISEASE

"The benefits of antiplatelet therapy for the prevention of thrombotic events in cardiovascular diseases are evident. Statistical studies have shown that secondary prevention by antiplatelet agents reduces the risk of nonfatal myocardial infarction (MI) and stroke by 25% to 30%, and the rate of vascular death by about 15%, resulting in a significant reduction in overall mortality" [65, 66]. These data demonstrate that (1) blood platelets, circulating in an activated state, are important determinants of arterial thrombus formation and vessel occlusion, and (2) these processes can be antagonized by appropriate antiplatelet therapy. However, it is also clear that one of the major problems in clinical use will be the separation of the anti-thrombotic efficacy of antiplatelet agents from interference with the physiological platelet function in hemostasis. Antiplatelet drugs are classified based on their site of action, that is, drugs that inhibit (i) platelet adhesion, (ii) platelet activation, (iii) platelet aggregation, and (iv) platelet mediated links with inflammation [65, 67]. "Aspirin belongs to the group of drugs that inhibit platelet activation. As highlighted before, platelet activation can be blocked by inhibiting the TXA2 pathway, ADP pathway, thrombin pathway, and phosphodiesterase (PDE). Aspirin meets its effects by inhibiting the TXA2 pathway in a dose-dependent manner. Low-dose (75-81 mg) Aspirin inhibits cyclooxygenase-1 (COX-1) so that only TXA2 production is inhibited and not of PGI2" [65, 68]. "Gastrointestinal tract (GIT) bleeding, drug interactions, and resistance are significant drawbacks of Aspirin. In an attempt to avoid these drug reactions, work is ongoing for new strategies such as inhibition of thromboxane synthetase enzyme and blockade of TXA2 receptors (TPRs). TXA2 synthetase is not much productive clinically because blockade of this enzyme results in the accumulation of endoperoxide precursors, which are platelet the TPR agonists" [65, 68].

## 8.0. SECONDARY PREVENTION

"Secondary prevention refers to Aspirin's use to prevent cardiovascular and cerebrovascular events in patients who have already experienced such an event or who have a high risk of a game," [69, 70]. "Long-term aspirin therapy reduces the yearly chance of serious vascular events (nonfatal myocardial infarction, nonfatal stroke, or vascular death), which corresponds to an absolute reduction of nonfatal events and a smaller, but still definite, reduction in vascular mortality" [69, 70]. "Against these benefits, the total increase in major gastrointestinal or other major extracranial bleeds is relatively lower. Hence, for secondary prevention, the benefits of aspirin therapy substantially exceed the risks, and Aspirin is recommended as secondary prevention in conjunction with lifestyle changes and stopping smoking from reducing an individual's overall risk of further cardiovascular events" [69, 70]. The Antithrombotic Trialists' (ATT) Collaboration performed a meta-analysis in 2002, which examined 287 randomized studies with 135000 high-risk patients in comparisons of antiplatelet therapy (predominantly Aspirin) versus control and 77000 in comparisons of different antiplatelet regimens [69, 70]. The results showed that among these high-risk patients, including acute MI, acute stroke, previous stroke or transient ischemic attack (TIA), peripheral arterial disease, atrial fibrillation, antiplatelet therapy reduced the combined outcome of any serious vascular event by about 25%, reduced nonfatal myocardial infarction by about 33%, reduced nonfatal stroke by about 25%, and reduced vascular mortality by about 17%. In each of the high-risk categories,



the absolute benefits outweighed the absolute risks of major extracranial bleeding [69, 70]. "For aspirin dosage choice, this analysis showed that COX is virtually completely inhibited in platelets, producing an anti-thrombotic effect within a few days of beginning 75 mg aspirin daily. It was indicated that high doses of 500– 1500 mg aspirin daily (which are more gastrotoxic) were no more effective than common treatments of 160–325 mg/day or low doses of 75–150 mg/day" [69, 70]. "Low-dose Aspirin (75–150 mg daily) is an effective antiplatelet regimen for long-term use, and the effects of doses lower than 75 mg daily were less specific. In acute clinical settings requiring an anti-thrombotic immediate impact (such as acute myocardial infarction, acute ischemic stroke, unstable angina), an initial loading dose of about 150–300 mg aspirin should probably be given" [69, 70]. "More recently, ATT Collaboration conducted another meta-analysis involving 16 secondary prevention trials (17 000 individuals at high average risk, 43 000 person-years, 3306 serious vascular events) that compared long-term Aspirin versus control" [69, 70]. "This analysis showed that aspirin allocation yielded a more significant absolute reduction in serious vascular events (6.7% versus 8.2% per year,  $P < 0.0001$ ), with a non-significant increase in hemorrhagic stroke but cutbacks of about 20% in total stroke (2.08% versus 2.54% Thrombosis 3 per year,  $P = 0.002$ ) and in coronary events (4.3% versus 5.3% per year,  $P < 0.0001$ ) [69, 71]. Aspirin (or another oral antiplatelet drug) is protective in most types of patient at increased risk of occlusive vascular events, including those with an acute myocardial infarction or ischemic stroke, unstable or stable angina, previous myocardial infarction, stroke or cerebral ischemia, peripheral arterial disease, or atrial fibrillation" [69, 70].

### 8.1 Secondary Prevention for Acute Coronary Syndromes

"The benefit of aspirin therapy for preventing cardiovascular events in patients with Acute coronary syndromes (ACS) (STEMI, USTEMI, UP) has been definitively demonstrated in several trials" [69, 72, 73]. "The previous meta-analysis by the ATT Collaboration reviewed 18788 patients with a history of MI from the 12 most important randomized clinical trials of Aspirin and showed that aspirin therapy reduced the relative risk of nonfatal MI by 28% ( $P < 0.0001$ ), vascular death by 15% ( $P < 0.0006$ ), and overall mortality by 11% ( $P = 0.02$ )" [69, 70]. The daily dosage of 80–325 mg appears to be effective in reducing cardiovascular events' risk. The 2007 ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation MI recommend initiating daily aspirin therapy with at least 162 mg as soon as possible after the clinical presentation, with 75–325 mg daily indefinitely after that [69, 74]. "The 2004 ACC/AHA guidelines for the management of patients with ST-segment elevation MI are similar but recommend 75– 162 mg daily as maintenance therapy after ST-segment elevation MI. Aspirin therapy is considered a class I recommendation (evidence supports that treatment is useful and sufficient) for all acute coronary syndromes" [69, 75]. The initial dose of Aspirin should be chewed and then swallowed during acute coronary syndromes to attain a rapid onset of action.

### 8.2 Secondary Prevention for Chronic Stable Angina

"A subgroup analysis of the U.S. Physicians' Health Study (PHS) of 333 men with chronic stable angina indicated that Aspirin reduced the relative risk of acute MI by 87% ( $P < 0.001$ )" [69, 76]. "The Swedish Angina Pectoris Aspirin Trial involved 2035 patients and found a 34% relative risk reduction in the occurrence of a first myocardial infarction

(MI) over a four-year follow-up period in patients receiving 75 mg of Aspirin daily, compared with patients receiving placebo" [69, 77]. "The 2002 ACC/AHA guidelines for chronic stable angina include a class IIa recommendation (the weight of evidence where opinion is in favor of usefulness and efficacy) for prophylactic aspirin therapy to prevent MI and death," [69, 78].

### 8.3 Secondary Prevention for Revascularization

"Aspirin has been widely accepted as a cornerstone therapy in reducing ischemic complications of coronary revascularization with coronary artery bypass graft surgery, balloon angioplasty, or stent implantation" [69, 79-81]. Several studies have demonstrated the efficacy of Aspirin in preventing thrombosis, a joint event following revascularization [69, 82-85].

"Aspirin administered in the immediate postoperative period following bypass surgery decreases the rate of graft occlusion by approximately 50%, and continued therapy leads to further decreases" [69, 79, 84]. "The use of Aspirin before and after the coronary intervention is essential in the prevention of thrombosis. Early trials indicated that, in patients undergoing PCI, Aspirin reduced mortality, MI, urgent revascularization, or stent thrombosis both with and without thienopyridines," [69, 86-88]. "The 2004 ACC/AHA guidelines for coronary artery bypass graft surgery suggest daily aspirin therapy with 100– 325 mg started within 24 hours after surgery" [69, 89]. "The 2005 ACC/AHA guidelines for percutaneous coronary intervention recommend 75–325 mg of Aspirin before the PCI procedure is performed in patients already taking daily chronic aspirin therapy, and 300–325 mg of Aspirin at least 2 hours and preferably 24 hours before the PCI procedure is performed in patients not already taking daily chronic aspirin therapy" [69, 90]. "After the PCI procedure, in patients with neither aspirin resistance, allergy, nor an increased risk of bleeding, Aspirin 162–325 mg daily should be given for at least one month after BMS implantation, three months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which daily chronic aspirin use should be continued indefinitely at a dose of 75 to 162 mg" [69, 90]. All of these recommendations belong to class I (evidence supports that treatment is useful and valid).

### 8.4 Secondary Prevention for Stroke and Transient Ischemic Attack

"The previous meta-analysis by the ATT Collaboration involved 18270 patients with a history of stroke or transient ischemic attack in 21 trials" [69, 70]. "The result showed that antiplatelet therapy (mainly Aspirin alone) for a mean duration of 29 months could significantly reduce the rate of major vascular events by 22%. Treating 1000 patients with a history of cerebrovascular disease for this duration will prevent about 36 vascular events, mostly nonfatal stroke recurrence (25 fewer per 1000 treated), and some nonfatal myocardial infarction (5 more infrequent per 1000)" [69, 70].

### 8.5 Secondary Prevention for Atrial Fibrillation

"The presence of atrial fibrillation (A.F.) gives rise to the development of atrial thrombus and consequently increases the risk of stroke among older adults. Vitamin K antagonists, most important among which is warfarin, significantly reduce the risk of stroke by almost two-thirds compared to placebo. Owing to the difficulties with using warfarin of its requirement for frequent monitoring of the international normalized ratio (INR) and increased hemorrhagic risk with increased duration of therapy, Aspirin has been considered a

potential alternate" [69, 91-93]. "Most of the evidence about aspirin therapy's effects among patients with atrial fibrillation was provided by the European atrial fibrillation trial" [69, 94]. "High-risk patients with a previous stroke or transient ischemic attack were randomized to Aspirin or placebo (or oral anticoagulant, if eligible). It was indicated that Aspirin is a safe, though less effective, alternative when anticoagulation is contraindicated. Besides, Aspirin prevents 40 vascular events for every 1,000 treated patients," [69, 70].

The previous meta-analysis by the ATT Collaboration included 2770 patients with atrial fibrillation in four trials and found a proportional reduction of about 9% to 24% in severe vascular events. In patients with "lone A.F.," who are under 65 years of age, not hypertensive, without evidence of cardiovascular disease and who have normal echocardiograms, the baseline stroke risk of this cohort is relatively low (approximately 0.5%/year). In this situation, Aspirin alone is considered by most experts to be adequate [69, 91-93].

## 9.0 PRIMARY PREVENTION

"For primary prevention, the balance between benefits and risks of aspirin use is less clear because the absolute benefits of Aspirin are generally lower than those in secondary prevention. Current guidelines largely ignore any differences in bleeding risk and recommend that Aspirin be used widely for primary prevention in those at moderately raised risk of coronary heart disease. It has also been suggested that, since age is a major determinant of the risk of coronary heart disease, daily Aspirin should be started in all people above a specific age, either alone or in combination with other drugs" [69, 94]. To date, six completed randomized trials have evaluated the benefits and risks of low-dose Aspirin for the primary prevention of cardiovascular disease. The British Male Doctors' Trial (BDT) [69, 95] of 5139 male physicians and the U.S. Physicians' Health Study (PHS) [26] of 22071 healthy male were completed during the late 1980s. The Thrombosis Prevention Trial (TPT) [69, 96] of 5085 men and the Hypertension Optimal Treatment (HOT) [69, 97] trial of 18790 (47% women) patients were completed in 1998. The Primary Prevention Project (PPP) [69, 98] study of 4495 (58% women) patients and the Women's Health Study (WHS) [69, 99] of 39876 healthy females were completed in the 2000s. In all these trials, patients were randomized to Aspirin and had follow-up durations ranging from 3.6 to 10.1 years. The PHS and BDT used aspirin regimens of 325 mg every other day and 500 mg/day, respectively, whereas the TPT and HOT used 75 mg/day of Aspirin and the PPP and WHS used 100 mg/day of enteric-coated Aspirin. "The Antithrombotic Trialists' (ATT) Collaboration undertook a meta-analysis in the six previous trials and found that, in the primary prevention trials, aspirin use yielded a 12% proportional reduction in serious vascular events (0.51% aspirin versus 0.57% control per year,  $P = 0.0001$ ), due mainly to about 20% reduction in nonfatal myocardial infarction (0.18% versus 0.23% per year,  $P < 0.0001$ )" [69, 71]. The net effect on stroke was not significant (0.20% versus 0.21% per year,  $P = 0.4$ : hemorrhagic stroke 0.04% versus 0.03%,  $P = 0.05$ ; other strokes 0.16% versus 0.18% per year,  $P = 0.08$ ). "Vascular mortality did not differ significantly (0.19% versus 0.19% per year,  $P = 0.7$ ). Aspirin use increased major gastrointestinal and extracranial bleeds (0.10% versus 0.07% per year,  $P < 0.0001$ ), and the main risk factors for coronary disease were also risk factors for bleeding. To better understand the impact of sex on the response to Aspirin, Berger and colleagues conducted a meta-analysis on the sex-specific benefits of Aspirin in 51342 women and

44114 men enrolled in the six previous prevention trials" [69, 100]. "The results demonstrate that aspirin therapy is associated with a significant reduction in the risk of cardiovascular events in both sexes. However, the specific types of benefits differ in important ways between women and men," [69, 100]. "Aspirin use in women was associated with statistically significant reductions in cardiovascular events (odds ratio [OR], 0.88 [CI, 0.79 to 0.99]) and ischemic strokes (OR, 0.76 [CI, 0.63 to 0.93]); no statistically significant benefit was found in the reduction of myocardial infarctions or cardiovascular mortality" [69, 100]. "In men, aspirin use was associated with a statistically significant reduction in cardiovascular events (OR, 0.86 [CI, 0.78 to 0.94]) and myocardial infarctions (OR, 0.68 [CI, 0.54 to 0.86]); no statistically significant benefit was found in the reduction of ischemic strokes or cardiovascular mortality" [69, 100]. "Total mortality was not significantly reduced by aspirin use in men or women. In summary, consistent evidence from randomized clinical trials indicates that aspirin use reduces the risk of CVD events in adults without a history of CVD," [69, 100]. "For primary prevention of cardiovascular disease, aspirin therapy significantly reduced the risk of the composite of cardiovascular events primarily by reducing the risk of ischemic stroke with no significant effect on the risk of MI in women and predominantly by reducing the risk of MI with no significant effect on the risk of stroke in men" [69, 100].

## 10.0 ASPIRIN RESISTANCE

Aspirin resistance can either be identified on clinical grounds or detected with laboratory tests that assess platelet activation [61].

**10.1 Clinical Aspirin resistance** is remarked as the drug's inability to prevent clinical atherothrombotic events in patients treated with Aspirin. Interestingly, the phenomenon is best described as aspirin treatment failure, because not all reports of atherothrombotic events take into account potential patient noncompliance [61, 65].

**10.2 Laboratory Aspirin resistance**, on the other hand, is defined as ASA failure to inhibit platelet aggregation predictably and measurably. It has been reported that 10-60% of aspirin therapy patients are resistant to Aspirin, and such patients are at risk of developing cardiovascular events [61, 101]. Although there may be several reasons for this, one that has attracted recent attention is increased expression of COX-2, which is hardly present in platelets under normal circumstances. It is speculated that COX-2 shows resistance to Aspirin in low-dose aspirin therapy because COX-2 has very low sensitivity to Aspirin. Besides, COX genes have more than 100 one-base substitutions, and it is suggested that some of them are associated with structural changes for which Aspirin cannot be sufficiently effective. In addition, genetic variations integrin, alpha 2b specifically in Chinese populations, has been suggested to be associated with insulin sensitivity [102]. Differences between individuals and ethnicity present a critical issue in clinical pharmacology [61, 101]. Aspirin resistance is also associated with excessive inflammation which is common in metabolic syndrome [103].

## 11.0 INDICATIONS FOR ASPIRIN

"The traditional primary use was for relief of pain and reduction of fever. Still, it was also recommended for use in rheumatoid arthritis, migraine, inoperable cancer, gout, rheumatic fever, acute tonsillitis, corns, and warts" [53-57]. "Aspirin is still the gold standard against which other analgesics, anti-inflammatory, and fever-reducing drugs have been measured. Indeed, Aspirin's success stimulated

the search for newer, more potent, and safer products — non-steroidal anti-inflammatory drugs (NSAIDs). Some of these are more potent than Aspirin, some are safer, and some (the recently introduced cyclooxygenase-2 [COX-2] inhibitors), are more specifically targeted at an enzyme level. Nevertheless, Aspirin remains a mainstay of analgesia. Of great interest is a marked reduction in colorectal cancer in habitual aspirin takers. This finding has been reported in many studies," [53-59]. "Low-dose Aspirin reduces the risk of a cardiovascular event, such as heart attack, stroke, or deep vein thrombosis, by about 30 percent [53, 54]. Aspirin equally reduces the risk of a cardiovascular event associated with Kawasaki disease [53, 60]. It has been more widely distributed than any other drug — Scott took it to the Antarctic, Hillary to Everest, and the astronauts to the moon," [53-57].

### 11.1 Newer Uses for Aspirin

The story of Aspirin is far from over, and according to Elwood *et al.* [53, 54], "several new uses of the drug are being investigated. Some of these arise from its anti-thrombotic effects, but others appear to originate from other drug actions. That Aspirin has other activities should not be surprising, because salicylates have many functions in plants that have nothing to do with platelets or thrombosis" [53, 54].

**11.1.1 Preeclampsia:** "There have been reports of a reduction in preeclampsia and retarded fetal growth in a number of small trials where subjects were given Aspirin, but these results remain controversial. If Aspirin is beneficial, this is likely to be because it reduces the risk of placental infarction. A significant trial was set up in an attempt to settle the controversy," [54, 104]. Although it gave no convincing evidence of benefit from Aspirin, uncertainty persists, particularly concerning interest on retarded fetal growth.

**11.1.2 Dementia:** A reduction in cognitive decline and dementia in patients who take Aspirin has been suggested. If confirmed, this will be of enormous importance to public health [54, 105]. "It seems likely that Aspirin might have some effect because a high proportion of dementia cases are caused by damage following a stroke or repeated, small, sub-clinical cerebral infarcts — multi-infarct dementia. Lesser degrees of damage from vascular lesions may also be prevented by low-dose Aspirin. Evidence from several trials is urgently needed, but results from one trial have already suggested benefit" [54, 105].

**11.1.3 Alzheimer's disease:** "Alzheimer's disease is another form of dementia. The etiopathogenesis of this disease is not thoroughly understood. Still, it is thought that the damage occurs through inflammatory processes around the so-called tangles that develop within the substance of the brain. Aspirin, even at low doses, has anti-inflammatory action. Therefore, it is not surprising that many observational studies have shown a reduced incidence of Alzheimer's disease in patients taking Aspirin or other anti-inflammatory drugs," [54, 106, 107].

**11.1.4 Cataracts:** "An association between regular aspirin taking and reduced development of cataracts has been reported. If real, this may be due to the inhibition of an enzyme within the lens tissues. Although regular aspirin benefits are likely to be modest, there seems to be a potentially substantial reduction in posterior subcapsular cataract, a particularly disabling subtype," [54, 108].

**11.1.5 Colorectal Cancer:** Of great interest is a marked reduction in colorectal cancer and other digestive tract

cancers in habitual aspirin takers. This finding has been reported in many studies [54, 109, 110]. "When diseased, some plants secrete salicylates to kill the affected parts and limit the disease's spread. Some works of literature may give a clue as to the mechanism of Aspirin in cancer. Therefore, it has been suggested that the drug may enhance the apoptosis of the cells involved in early cancer within human subjects. Several trials have been set up in patients with familial polyposis and in other high-risk groups to determine whether this is the case," [54, 109, 110].

#### 11.1.6 Low-dose Aspirin in cardiovascular disease:

Aspirin reduces the risk of a cardiovascular event, such as heart attack, stroke, or deep vein thrombosis, by about 30 percent. If a thrombosis does occur in patients on low-dose Aspirin, the infarct is likely to be less dangerous. The absolute reduction in risk is dependent on the patient group: a) Three events per hundred per year in patients at high risk; b) Three events per thousand per year in healthy subjects at low risk. The reduction in risk is dependent upon compliance. The benefit obtained from erratic doses is substantially less than that from a regular daily dose [54].

**11.1.7 Kawasaki disease:** "Aspirin equally reduces the risk of a cardiovascular event associated with Kawasaki disease; which is an acute vasculitis in young children and causes coronary artery abnormalities (CAAs) such as coronary artery aneurysm and dilation, is the leading cause of acquired heart disease in children in developed countries" [111-113]. "In the five decades since the initial recognition of K.D., the standard treatment is a combination of intravenous immunoglobulin (IVIG) and acetylsalicylic acid (ASA)," [111, 114]. "High-dose (80–100 mg/kg) and medium-dose (30–50 mg/kg) ASA have been recommended as standard treatment during the acute febrile phase by the American Heart Association (AHA) and Japanese Society of Pediatric Cardiology and Cardiac Surgery (JSPCCS)" [111, 115, 116].

## 12.0 ADVERSE EFFECTS

### 12.1 Contraindications

Aspirin should not be taken by people who are allergic to ibuprofen or naproxen, [117, 118], or salicylate intolerance [119, 120] or more generalized drug intolerance to NSAIDs, and caution should be exercised in those with asthma or NSAID-precipitated bronchospasm. Owing to its effect on the stomach lining, manufacturers recommend people with peptic ulcers, mild diabetes, or gastritis to seek medical advice before using aspirin [116, 120]. Even if none of these conditions is present, the risk of stomach bleeding is still increased when Aspirin is taken with alcohol or warfarin [116, 120]. People with hemophilia or other bleeding tendencies should not take Aspirin or other salicylates [117, 121]. "Aspirin is known to cause hemolytic anemia in people who have the genetic disease glucose-6-phosphate dehydrogenase deficiency, particularly in large doses and depending on the severity of the disease" [122]. The use of Aspirin during dengue fever is not recommended owing to increased bleeding tendency [123]. "People with kidney disease, hyperuricemia, or gout should not take Aspirin because it inhibits the kidneys' ability to excrete uric acid, thus may exacerbate these conditions. Aspirin should not be given to children or adolescents to control cold or influenza symptoms, as this has been linked with Reye's syndrome" [124].

#### 12.1.1 Gastrointestinal Effects

Aspirin use has been shown to increase the risk of gastrointestinal bleeding [125]. Although some enteric-

coated formulations of Aspirin are advertised as being “gentle to the stomach,” in one study, the enteric coating did not seem to reduce this risk [125]. Combining Aspirin with other NSAIDs has also been shown to increase this risk further [125]. Using Aspirin in combination with clopidogrel or warfarin also increases the risk of upper gastrointestinal bleeding [126]. Blockade of COX-1 by aspirin results in the upregulation of COX-2 as part of a gastric defense [127] and that taking COX-2 inhibitors concurrently with Aspirin increases the gastric mucosal erosion [128]. Therefore, caution should be exercised if combining Aspirin with any “natural” supplements with COX-2- inhibiting properties, such as garlic extracts, curcumin, bilberry, pine bark, ginkgo, fish oil, resveratrol, genistein, quercetin, resorcinol, and others. In addition to enteric coating, “buffering” is the other leading method companies have used to try to mitigate the problem of gastrointestinal bleeding. Buffering agents are intended to work by preventing the Aspirin from concentrating on the stomach walls, although the benefits of buffered Aspirin are disputed. Almost any buffering agent used in antacids can be used; Buffering for example, uses magnesium oxide. Other preparations use calcium carbonate [129]. “Taking it with vitamin C has been investigated as a method of protecting the stomach lining. Taking equal doses of vitamin C and Aspirin may decrease the amount of stomach damage compared to taking Aspirin alone,” [130, 131].

### 12.1.2 Central Effects

Large doses of salicylate, a metabolite of Aspirin, cause temporary tinnitus (ringing in the ears) based on rats' experiments, via the action on arachidonic acid and NMDA receptors cascade [132].

### 12.1.3 Reye's Syndrome

Reye's syndrome, a rare but severe illness characterized by acute encephalopathy and fatty liver, can occur when children or adolescents are given Aspirin for a fever or other disease or infection. From 1981 to 1997, 1207 cases of Reye's syndrome in people younger than 18 were reported to the U.S. Centers for Disease Control and Prevention. Of these, 93% reported being ill in the three weeks preceding the onset of Reye's syndrome, most commonly with a respiratory infection, chickenpox, or diarrhea. Salicylates were detectable in 81.9% of children for whom test results were reported [133]. “After the association between Reye's syndrome and Aspirin was reported; Safety measures to prevent it (including a Surgeon General's warning, and changes to the labeling of aspirin-containing drugs) were implemented, Aspirin taken by children declined considerably in the United States, as did the number of reported cases of Reye's syndrome. A similar decline was found in the United Kingdom after warnings against pediatric aspirin use were issued” [133]. “The U.S. Food and Drug Administration recommends Aspirin (or aspirin-containing products) should not be given to anyone under the age of 12 who has a fever, [124]. The U.K. National Health Service recommends that children under 16 years of age should not take Aspirin unless it is on the advice of a doctor” [134].

For a small number of people, taking Aspirin can result in symptoms resembling an allergic reaction including hives, swelling, and headache [135]. The reaction is caused by salicylate intolerance and is not a true allergy, but rather an inability to metabolize even small amounts of Aspirin, resulting in an overdose. Aspirin and other NSAIDs, such as ibuprofen, may delay the healing of skin wounds [136]. However, Aspirin may heal venous leg ulcers that have not healed following the usual treatment [137].

## 12.2 Other Adverse Effects

“Aspirin can induce swelling of skin tissues in some people. In one study, angioedema appeared one to six hours after ingesting Aspirin in some of the people. However, when the Aspirin was taken alone, it did not cause angioedema in these people; the Aspirin had been taken in combination with another NSAID-induced drug when angioedema appeared” [138]. “Aspirin causes an increased risk of cerebral microbleeds having an appearance on MRI scans of 5 to 10 mm or smaller, hypointense (dark holes) patches) Such cerebral microbleeds are important since they often occur before ischemic stroke or intracerebral hemorrhage, Binswanger disease, and Alzheimer's disease” [139, 140].

“In one research study, with a mean dosage of Aspirin of 270 mg per day, there was an estimated absolute risk increase in intracerebral hemorrhage (ICH) of 12 events per 10,000 persons” [141].

In comparison, the estimated absolute risk reduction in myocardial infarction was 137 events per 10,000 persons, and a discount of 39 events per 10,000 persons in ischemic stroke [141]. In cases where ICH already has occurred, aspirin use results in higher mortality, with a dose of about 250 mg per day resulting in relative risk of death within three months after the ICH around 2.5 (95% confidence interval 1.3 to 4.6) [142]. “Aspirin and other NSAIDs can cause abnormally high blood levels of potassium by inducing a hyporeninemic hypoaldosteronism state via inhibition of prostaglandin synthesis; however, these agents do not typically cause hyperkalemia by themselves in the setting of normal renal function and euvolemic state” [143].

Moreover, “Aspirin can cause prolonged bleeding after operations for up to 10 days. In a study, 30 of 6499 people having elective surgery required reoperations to control bleeding. Twenty had diffuse bleeding, and 10 had bleeding from a site, scattered, but not discrete, bleeding was associated with the preoperative use of Aspirin alone or in combination with other NSAIDs in 19 of the 20 diffuse bleeding people” [144]. On 9 July 2015, the FDA toughened warnings of increased heart attack and stroke risk associated with non-steroidal anti-inflammatory drugs (NSAID). Aspirin is an NSAID but is not affected by the new signs [145].

## 12.3 Drug Overdose

“Aspirin overdose can be acute or chronic. In acute poisoning, a single large dose is taken; in chronic poisoning, higher than regular treatments are taken over time. Acute overdose has a mortality rate of 2%. Chronic overdose is more commonly lethal, with mortality rate of 25%,” [146] chronic overdose may be especially severe in children [147]. Toxicity is managed with potential treatments, including activated charcoal, intravenous dextrose, normal saline, sodium bicarbonate, and dialysis [148]. “The diagnosis of poisoning usually involves the measurement of plasma salicylate, the active metabolite of Aspirin, by automated spectrophotometric methods. Plasma salicylate levels in the wide range from 30–100 mg/l after usual therapeutic doses, 50–300 mg/l in people taking high doses, and 700– 1400 mg/l following acute overdose. Salicylate is also produced as a result of exposure to bismuth subsalicylate, methyl salicylate, and sodium salicylate” [149, 150].

## 12.4 Interactions

“Aspirin is known to interact with other drugs. For example, acetazolamide and ammonium chloride are known to enhance the intoxicating effect of salicylates, and alcohol also increases the gastrointestinal bleeding associated with

these types of drugs" [118, 119]. "Aspirin is known to displace several drugs from protein-binding sites in the blood, including the antidiabetic drugs tolbutamide and chlorpropamide, warfarin, methotrexate, phenytoin, probenecid, valproic acid (as well as interfering with beta-oxidation, an important part of valproate metabolism), and other NSAIDs. Corticosteroids may also reduce the concentration of Aspirin. Ibuprofen can negate the antiplatelet effect of Aspirin used for cardioprotection and stroke prevention" [151]. "The pharmacological activity of spironolactone may be reduced by taking aspirin, and it is known to compete with penicillin G for renal tubular secretion" [152]. Aspirin may also inhibit the absorption of vitamin C [153-155].

### 13.0 ASPIRIN - SAFER FORMULATIONS

Several pharmacological manipulations of Aspirin have been made to decrease the gastric toxicity of the drug. For instance, sustained-release [156, 157] and topical formulations [156, 157] demonstrating evidence-based selective inhibition of platelet TXA<sub>2</sub> production; but, with minimal effects on vascular and gastric prostanoids. These formulations, therefore, are resulting in less gastrototoxicity generally [156, 158].

Furthermore, "enteric-coated aspirin tablets discovery was aimed at reducing the gastric irritation associated with the consumption of Aspirin, thus, may be less gastrototoxic in action" [156, 159]. "In one endoscopic study of asymptomatic patients undergoing long-term aspirin therapy gastric mucosal erosions were noted in 90% of patients treated with regular Aspirin compared with 60% of patients receiving enteric-coated Aspirin. Besides, G.I. blood loss is less with enteric-coated Aspirin than with the non-coated formulation," [156, 159]. "Interestingly, the mechanism of action of enteric-coated Aspirin still leads to the systemic inhibition of COX. Therefore, coated Aspirin is associated with significant gastric toxicity compared with placebo" [156, 159], and results in a similar risk of upper G.I. bleeding compared with regular, uncoated Aspirin [156, 160, 161]. Daily Aspirin is rapidly absorbed from the stomach's acid environment, and enteric coating of aspirin results in its release into the alkaline environment of the small bowel, where it is hydrolyzed. As a result, enteric-coated Aspirin has lower bioavailability than regular Aspirin [156, 162].

"Nonetheless, the antiplatelet effects of full-dose (300 mg) enteric-coated Aspirin are similar to those of uncoated formulations," [156, 162, 163]. "However, the efficacy of low-dose (100 mg) enteric-coated preparations has not been clearly established, and such doses may result in inadequate platelet inhibition. Thus, if coated Aspirin is prescribed, larger doses may be necessary to obtain the desired antiplatelet effect. The dissociation of the effects of the different COX enzymes (COX-1 and COX-2), has stimulated the production of agents that preferentially inhibit COX-2 and allow for the inhibition of inflammatory prostaglandins while leaving homeostatic prostaglandins relatively intact" [156, 162, 163].

In a related development, several new NSAIDs have been shown to have relative COX-2 selectivity [156, 164-166] and appear to be associated with fewer gastric side effects [156, 167, 168]. "The anti-thrombotic therapeutic impact and the toxic gastric effects of Aspirin are mediated through the inhibition of COX-1; therefore, dissociation of these effects is not feasible. However, co-administration of Aspirin with the synthetic PGE<sub>2</sub> analog misoprostol allows for the complete inhibition of TXA<sub>2</sub> synthesis in platelets while maintaining gastric protection. This approach decreases the risk of gastric ulceration, erosion, and bleeding in dogs," [156, 169,

170]. "Furthermore, in a randomized trial in healthy volunteers given anti-inflammatory doses of Aspirin (3900 mg/d), co-treatment with 200 mg of misoprostol twice daily significantly reduced endoscopically documented gastric and duodenal mucosal injury (P,0.006)" [156, 171]. "Other novel methods of improving the safety profile of Aspirin are being developed. Animal models suggest that the intragastric administration of Aspirin stimulates the release of NO, which decreases gastric acid secretion and increases cytoprotection, thus limiting gastric mucosal damage," [156, 172].

"Moreover, compared with regular Aspirin, the administration of NO-releasing derivatives of Aspirin has no topical gastric irritating effects, does not worsen stress-induced gastric ulceration, and protects against toxic gastric injury" [156, 173-175]. "This marked improvement in gastric toxicity occurs with these agents despite the equivalent inhibition of COX and equipotent or enhanced anti-thrombotic activity compared with aspirin" [156, 175]. The clinical safety and efficacy of these agents remain to be determined.

### 14.0 KEY PANEL MESSAGES

1. The therapeutic benefits of Aspirin were widely recognized, and over time, other drugs were developed that had the same anti-inflammatory, analgesic, and antipyretic activities.
2. Aspirin has been used for over a century to treat the cardinal signs of inflammation (heat, redness, swelling, and pain). In contrast, recently, it has been shown to prevent intravascular thrombosis and cancer and slow Alzheimer's disease.
3. The biochemistry and pharmacology of Aspirin with particular emphasis on its cyclooxygenase-dependent and independent cyclooxygenase effects in platelets was exhaustively discussed.
4. No other drug is so inexpensive and has such abundant scientific evidence of its clinical efficacy.
5. The discussion emphasized recent advances in platelet proteomics targets of aspirin-mediated acetylation in platelets that may play a role in its chemopreventive mechanism.
6. Low doses aspirin result in selective inhibition in platelet Thromboxane A<sub>2</sub> production without suppressing prostacyclin (PGI<sub>2</sub>), a common platelet antagonist, and vasodilator.
7. Aspirin reduces the risk of a cardiovascular event, such as heart attack, stroke, or deep vein thrombosis, by about 30 percent. If a thrombosis does occur in patients on low-dose Aspirin, the infarct is likely to be less dangerous.
8. Aspirin has been associated with a reduced risk of colorectal cancer, and possibly a few other digestive tract cancers.
9. Current evidence further quantifies the inverse association between regular aspirin use and the risk of colorectal and other digestive tract cancers, including some rare ones. The favorable effect of Aspirin increases with longer duration of use, and, for colorectal cancer, with increasing dose.
10. Several efforts are in place to produce safer formulation to reduce the unwanted adverse effects of Aspirin.

- The emerging future interest is to establish evidence for Aspirin as the novel therapeutic drug for combating severe acute inflammation and thrombosis associated with the cytokine storm in COVID-19 patients.

## 15.0 CONCLUSIONS AND FUTURE DIRECTIONS

Aspirin, initially developed as an analgesic, antipyretic and anti-inflammatory agent, has come to be the basis of antiplatelet therapy, and firm evidence supporting its usefulness has continued to accumulate. Because of its antiplatelet activity for the prevention and treatment of thrombosis, aspirin is one of the most commonly used drugs in the world. However, it has been reported that only one-fourth of all patients with coronary artery disease amenable to aspirin therapy currently use it. If the administration of aspirin to suitable patients is increasingly promoted as recognition by general clinicians is enhanced, aspirin will undoubtedly become the most frequently used drug in the world. No other drug is so inexpensive and has such abundant scientific evidence of its clinical efficacy.

Furthermore, new questions are arising as the understanding of aspirin deepens, and the potential of its diverse efficacy is staggering. Aspirin, therefore, is not only a well-established therapeutic agent but also an exciting new drug. The emerging future interest is to establish evidence for Aspirin as the novel therapeutic drug for combating severe acute inflammation and thrombosis associated with the cytokine storm in COVID-19 patients. Notably, a randomized clinical trial, to test a range of potential treatments for COVID-19, includes low-dose Aspirin as anti-inflammatory and antiplatelet treatment.

## DECLARATION

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