REVIEW ARTICLE

RECENT ADVANCEMENTS IN
THE CLINICAL USE OF ASPIRIN

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ABSTRACT
Aspirin (acetylsalicylic acid) is a widely used drug that possesses analgesic activity. It is effective in the treatment of pain, inflammation and fever. In addition to these ailments aspirin has been found to be useful in the treatment of other diseases including cell apoptosis and colorectal cancer, Kawasaki disease, migraine and cardiovascular diseases. The mechanism of action of aspirin is due to its ability to suppress the production of prostaglandin and thromboxanes as a result of its irreversible inactivation of cyclo-oxygenase (COX) enzyme. The recent advancements in these fields have been reviewed in this article.

Key words: Aspirin, cancer, cardiovascular disease, fever, diabetes, Kawasaki disease.

1. INTRODUCTION
Aspirin is one of the most widely used analgesic drug belonging to the salicylate group of compounds and is chemically known as acetylsalicylic acid\textsuperscript{1,2}. In the mid of 19th century with the discovery of salicylates, the active components of Willow Spp., enabled the synthesis of other derivatives from salicylates like aspirin\textsuperscript{3}. It was first prepared in 1853 and its pharmacological activities were discovered in 1899\textsuperscript{4,5}. Aspirin was firstly used as a medicine in 1899 by Dreser\textsuperscript{6}.

2. SYNTHESIS
The synthesis of aspirin is achieved by the esterification reaction. Salicylic acid is treated with acetic anhydride, causing a chemical reaction that turns salicylic acid's phenol group into an acetyl group, (R-OH R-OCOCH\textsubscript{3}). This process yields aspirin and acetic acid, the later is considered as a byproduct of this reaction\textsuperscript{7} as shown in Fig. 1.

![Fig. 1. Synthesis of aspirin.](image)

3. BIOLOGICAL DATA
The biological data on aspirin dealing with plasma half-life, LD\textsubscript{50}, volume of distribution, protein binding, absorption, secretion and dose are given in Table 1.

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>pK\textsubscript{a}</th>
<th>Plasma Half-life</th>
<th>Toxicity LD\textsubscript{50}</th>
<th>Volume of Distribution</th>
<th>Protein Binding</th>
<th>Absorption and Excretion</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetyl-salicylic acid</td>
<td>3.5</td>
<td>About 17 min\textsuperscript{8}</td>
<td>Orally in mice, rat g/kg 1.1-1.5\textsuperscript{9}</td>
<td>About 0.15 L/kg\textsuperscript{8}</td>
<td>90 %\textsuperscript{8}</td>
<td>Oral absorption &gt;80%, presystematic metabolism high, bioavailability rapid\textsuperscript{10} excretion in urine about 50-80 %\textsuperscript{8}</td>
<td>Usually 1.2-4.0 g up to 8.0 g daily in rheumatic disorders\textsuperscript{8}. 325-650 mg q-4 h as an analgesic. 300-325 mg/day in MI, 1.3 g/day for stroke\textsuperscript{11}.</td>
</tr>
</tbody>
</table>

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4. CLINICAL USE
Aspirin is effective in the treatment of pain, inflammation and fever, and has extensive use for the prevention of cardiovascular diseases. The various important clinical applications of aspirin are discussed in the following sections.

4.1. Cell Apoptosis and Colorectal Cancer
Colorectal cancer (CRC) and colorectal adenomas are actually a dysfunction of Adenomatous Polyposis Coli suppressor gene (APC)\textsuperscript{12}. CRC is the most common neoplasia in western countries and second leading cause of cancer related deaths\textsuperscript{13}. Aspirin has shown new advancements in its therapeutic uses, such as the cell apoptosis, chemoprevention of colorectal cancer and the prevention and treatment of Kawasaki disease\textsuperscript{14}.

Aspirin alone has been found to lower the risk of at least nine common cancers over 20\%, and as high as 70\%. Aspirin has also been found as a beneficial chemopreventive and chemotherapeutic agent with lower toxicity\textsuperscript{15}. A dose-dependent reduction in cell viability was observed in colorectal cancer cells treated with aspirin and there is a potential risk reduction of 40-50\% especially in individuals at higher risk of polyposis\textsuperscript{16}. Other studies have shown a beneficial effect on the prevention of colonic and other GI cancers with long term use of aspirin\textsuperscript{17}. CRC has been rated as the third most commonly spread cancer in UK and the role of non-steroidal anti-inflammatory drugs (NSAIDs) has been a very cost effective therapy in the prevention of CRC\textsuperscript{18}. Aspirin has also been found to be beneficial in the treatment and prevention of CRC\textsuperscript{19, 20}. A meta-analysis of randomized trial has indicated that non-vascular deaths including cancer were reduced with low dose aspirin treatment up to 2.58\%\textsuperscript{21}. Another study reported that the use of daily aspirin was helpful for lowering the risk of long term incidence of some adenocarcinomas and also reduced the growth of distant metastasis\textsuperscript{22}. Aspirin has been found to be a beneficial adjuvant treatment in CRC in terms of availability and cost effectiveness\textsuperscript{23}. The studies have been showed that aspirin reduces the onset of advanced adenomas up to 28\% and any type of adenoma up to 17\%\textsuperscript{24}. In randomized control trials (RCTs) of CRC reoccurrence in patients with hereditary CRC syndrome has been found to be reduced with the use of aspirin. This study also describes the safety and mechanism of aspirin action in CRC prevention\textsuperscript{25}. The pharmacology and the mechanism of action of aspirin and non-aspirin NSAIDs in CRC by inhibiting cyclooxygenase (COX)-2 and PGE (2) formation has been discussed\textsuperscript{12}. The chemoprevention due to COX-2 inhibition has been proved in CRC\textsuperscript{13, 26, 27}. The pooled analysis of randomized trials for daily use of aspirin has shown a substantial reduction of cancer mortality and improvement by long term use of aspirin\textsuperscript{28}. Aspirin doses ranging from 81-325 mg/d tested among the patients having an average age of 58 years in which 60\% were male with follow up of 3 months, showed the effectiveness of aspirin in CRC patients with advanced lesions by reducing the CRC risk about 6.7\%\textsuperscript{29}.

4.2. Kawasaki Disease
Kawasaki disease (KD) is an autoimmune syndrome\textsuperscript{30} and is also known as Kawasaki syndrome (KS), lymph node syndrome and muco-cutaneous lymph syndrome\textsuperscript{31}. It has been found as an acute systemic vasculitis syndrome of childhood; mostly affecting the children younger than five years of age\textsuperscript{32, 33, 34}. The etiology of KD is unknown, symptoms include fever, conjunctival injection, exanthem, exanthema, erythema of the lips and oral mucosa, rashes, swelling of hands and feet and cervical lymphadenopathy\textsuperscript{35, 36}. The most fatal effect of this disease on untreated children is found to be coronary artery aneurysms\textsuperscript{30}.

Aspirin has been found to be the basic supportive treatment in KD. A comparison of duration of fever, transaminase, plasma thromboxane B\textsubscript{2} (TxB\textsubscript{2}) and 6-ketoprostaglandind F\textsubscript{1alpha} (PGF\textsubscript{1}) levels has shown
that a low dose treatment with aspirin is beneficial and safe in the acute stage of KD, instead of higher dose which might cause the antithrombotic effect. The use of aspirin in KD treatment seems to be significant because of its antipyretic and antiplateletic activity which has been found as a long term prophylaxis against coronary artery aneurysms. The treatment regimen of aspirin is started with a high dose for its anti-inflammatory effect and then continued with low dose for its antithrombotic activity. The adjuvant therapy of aspirin with intravenous gamma globulin (IVGG) has been found to be beneficial by improving the functions of circulating endothelial progenitor cells (EPCs) in children by inhibiting the plasma Tumor Necrosis Factor-α (TNF-α) and high sensitivity C-Reaction Protein (hs-CRP) level. In the IVGG treatment, high dose of aspirin has been found to be of little benefit to treat the acute phase of KD due to its antipyretic effect although it has no influence on IVGG response or other manifestations.

4.3. Migraine
Migraine is a frequent, disabling condition for the individual, health services and society. Migraine is usually a self-limited, recurrent severe headache linked with autonomic symptoms. About 15-30% of people with migraine experience the disease with an aura. Aspirin is the first line therapy for acute migraine headaches in adults. It has also been found to relieve the migraine attack in about 44% patients. The tension-type headache and migraine is the most common primary headaches. The majority of patients with these two types of headaches have been treated with over-the-counter analgesics or NSAIDs. The scientific data available for randomized, placebo-controlled trials indicate that aspirin, ibuprofen, ketoprofen, diclofenac and naproxen have been useful in tension-type and migraine headache. Aspirin is also first-line treatment for episodic tension-type headache regardless of headache intensity. NSAIDs and the combination of analgesics containing acetaminophen, aspirin and caffeine (AAC) have been used as a first-line treatment for mild to moderate migraine. Another study has indicated that the combination of AAS was more efficient and better to monotherapy with the individual drug in the combination for the migraine and tension-type headache therapy. Intravenous aspirin (lysine acetylsalicylate) is a safe and useful treatment for the management of acute migraine attacks in hospitalized patients. A comparative meta-analysis study in individual patients with three trials in migraine headache has indicated that 1000 mg effervescent aspirin is effective against 50 mg sumatriptan for the treatment of acute migraine attacks with fewer side effects. Aspirin has been as effective as triptans for treating moderate to severe migraine pain. It has also been found as an effective analgesic due to various pain causes especially in acute post-operative pain. The non-prescription combination of AAC has been found to be very effective in the treatment of severe disabling migraine attack and the above combination (AAC) is also found to be beneficial for the treatment of migraine associated with menstruation. A double-blind, randomized, parallel group, multicentre placebo controlled single dose comparison study of a combination of AAC to that of ibuprofen has been found to be a safe and cheaper treatment as well as the combination has also found to be more effective in terms of onset of action.

4.4. Fever/Antipyretic Effect
Fever is a complex physiologic response caused by any infection or aseptic stimuli which may lead to increase in the body temperature. This increase body temperature is due to the increase concentrations of prostaglandin E(2) (PGE(2)). Salicylates, aniline derivatives such as acetaminophen, and nonacidic pyrazolones have been used for almost 100 years as the most important antipyretic agents. NSAIDs have an anti-inflammatory, analgesic, and antipyretic properties. Aspirin has shown a useful indication for its antipyretic activity. The ability of aspirin
to reduce the fever is due to its action on the prostaglandin system through its irreversible inhibition of COX system\textsuperscript{62}. Another study has been described the comparison of naproxen and aspirin for its antipyretic activity and shown that the effectiveness of naproxen is similar to aspirin in terms of onset of action and in fever reduction\textsuperscript{63}.

4.5. Diabetes

In the U.S. almost every adult with diabetes has at least one risk factor for cardiovascular disease (CVD) and thus aspirin treatment is beneficial for the above\textsuperscript{64}. Patients with diabetes have shown altered platelet function with increased production of thromboxane\textsuperscript{65,66}. CVD is the major cause of complications and death in patients with diabetes and aspirin has been found as an effective treatment for patients with preexisting coronary disease\textsuperscript{67}. Use of aspirin among patients with diabetes has increased from 37.5\% in 1997 to 48.7\% in 2001\textsuperscript{68}. Comparisons of patients with same age and sex with diabetes and without diabetes mellitus (DM) have shown increase risk of cardiovascular events up to two to four times as compared with patients without the disease. Risk of deaths in patients aged older than 65 years is more than two-thirds with diabetes associated coronary heart disease (CHD)\textsuperscript{69}. In diabetic patients 68\% of deaths over the age of 65 years are due to the CHD and 16\% are from stroke\textsuperscript{70}. Aspirin is recommended for secondary prevention in diabetes and macrovascular disease\textsuperscript{71,72}. Reason of CVD in most of the DM patients is due to the formation of less permeable fibrin network. This study have been indicated that a high dose aspirin treatment is effective to improve the permeability of fibrin network in DM patients which ultimately beneficial for the prevention of CVD risk\textsuperscript{73}.

The use of combination therapy of aspirin, statin and a blood pressure lowering agents (polypill) have shown the increase lower risk of vascular morbidity and mortality\textsuperscript{74}. The role of aspirin in lowering the risk of myocardial infarction, stroke and death is well known in DM patients with CVD but the use of aspirin as a primary treatment for CVD associated DM is still unclear\textsuperscript{75,76,77}. Aspirin could be beneficial for the prevention of severe diabetic retinopathy which may leads to blindness\textsuperscript{78,79}. In the another study, it has been found that high doses of aspirin and intermediate doses of COX-2 inhibitors decrease leukocyte adhesion and blood–retinal barrier breakdown through the inhibition of NF-κ B activation and TNF-α production. NSAIDs like meloxicam and aspirin have been beneficial in different inflammatory diseases. NSAIDs have shown effective prevention in early diabetic retinopathy and important in clinical efficacy in patients\textsuperscript{80}.

4.6. Pre-eclampsia

Pre-eclampsia is a multisystem disorder mostly associated with increased blood pressure and proteinuria\textsuperscript{81}. It is a major worldwide cause of maternal, neonatal and perinatal mortality\textsuperscript{82}. Aspirin treatment started in early pregnancy is found to be most beneficial in lowering the prevalence of preeclampsia in women\textsuperscript{83,84}. A meta-analysis has been conducted in the women with increased risk of preeclampsia to evaluate the effect of gestational age with aspirin therapy with ultrasonographic evidence of abnormal placentation diagnosed by uterine artery Doppler studies. Nine randomized controlled trials have been done with a total of 1317 women. Results have been shown that there was a great reduction in the incidence of pre-eclampsia when treatment of aspirin is started in early gestation as compared to treatment in late gestation. Aspirin treatment started at less or equal to 16 weeks' gestation found to be a relative risk (RR) of 0.48, at 17-19 weeks RR 0.55 and at greater or equal to 20 weeks RR 0.82 (with confidence interval (CI) 95\%)\textsuperscript{82}. It has been suggested that the low daily doses of aspirin taking in the third trimester of pregnancy reduced the incidence of pregnancy-induced hypertension and preeclamptic toxiemia might be by balancing the levels of thromboxane and prostacyclin in women\textsuperscript{85}. A similar systematic
review and meta-analysis of randomized controlled trials have been conducted in women with less than or equal to 16 weeks' gestation. Treatment with low-dose aspirin started at less or equal to 16 weeks of gestation have showed the reduction of the risk of severe preeclampsia, but not mild preeclampsia. A systemic review has been done to compare the effect of early administration of aspirin on the risk of preterm and term preeclampsia. Randomized controlled trials have been conducted in female patients with low-dose aspirin or placebo/no treatment at or before 16 weeks of gestation showing decrease incidence of preterm but not term preeclampsia. In another study a randomized, double-blinded, placebo-controlled trial has been done, it has been found that there is no statistically considerable effect in preventing pre-eclampsia with aspirin therapy in high-risk women but aspirin might be decrease the incidence of pre-eclampsia.

4.7. Cardiovascular Diseases (CVD)

CVD is arising as one of the most important worldwide health related problem especially in developed countries. According to World Health Organization (WHO), at the end of year 2020, CVD will become the primary cause of death and disability worldwide. For the prevention and treatment of CVD, daily low dose aspirin has found to be recommended for the patients worldwide. Aspirin has been found to reduce the risks of CVD and also in secondary prevention like in acute myocardial infarction (MI), acute occlusive stroke, as well as in primary prevention and found to be very significant statistically and clinically for the reduction of above stated complications and also reduce the incidence of premature deaths due to MI and strokes alone or in combination with statin.

Aspirin has been found to possess a potential antiplatelet activity by irreversibly inactivated cyclooxygenase-1 (COX1), which may lead to the inhibition of thromboxane A2 synthesis. Aspirin has been known for its immediate and long term antithrombotic effect because platelets do not reproduce the COX. Aspirin has found to be good in atherosclerosis as it also inhibits the production of COX-dependent vasoconstrictors which may lead to the endothelial dysfunction. A high dose of IVGG in combination with aspirin has been found considerable reduction in the frequency, severity and intensity of cardiovascular complications. Aspirin shows remarkable benefit in coronary angioplasty which lead to 53% (P < 0.0002) reduction in myocardial infarction, stroke or fatal deaths due to CVD. Some major CVD problems in which aspirin therapy plays a significant role have been discussed below:

4.7.1. Myocardial Infarction

Myocardial infarction (MI) is the medical terminology which commonly known as a heart attack, symptoms include sudden chest pain which sometimes radiate to the left arm or the left side of the neck, shortness of breath, anxiety, sweating, nausea, vomiting and abnormal heartbeats. Different previous and recent trials have been showed that low-dose aspirin considerably reduce the risk of MI and other cardiovascular events as it reduce the incidence of deep venous thrombosis and pulmonary embolism. Aspirin has been found as an effective treatment when given as an adjunct to manage cardiovascular risk factors and found effective for the prevention of large number of premature deaths and MIs. Patients with a history of cardiovascular disease, if did not continue the low dose aspirin treatment have high risk of non-fatal myocardial infarction as compared with those who continued the treatment. A nested case-control study has been conducted for 3.2 years to identify cases of non-fatal myocardial infarction or death from coronary heart disease. The results showed that among 1222 patients, 876 were of non-fatal myocardial infarctions and 346 deaths are due to coronary heart disease. The results have been compared in patients who had recently discontinued aspirin treatment had a considerably increased risk.
of non-fatal myocardial infarction or death from coronary heart disease combined showed the rate ratio of $1.43$, $95\%$ CI $1.12$ to $1.84$ and for non-fatal myocardial infarction alone the rate ratio is $1.63$, with CI $1.23$ to $2.14$\textsuperscript{103}. Antiplatelet drugs such as aspirin alone or in combination with clopidogrel have been continuously used to reduce the risk of plaque rupture and recurrent myocardial infarction. As compare to clopidogrel, aspirin is used as first choice due to its efficacy and cost effectiveness\textsuperscript{104}. Aspirin (325 mg) with clopidogrel (600 mg) should be given to the pregnant patients having acute myocardial infarction (AMI) with atherosclerotic disease and for revascularization either balloon angioplasty or bare metal stent should be used\textsuperscript{105}.

4.7.2. Angina

Antiplatelet has been found as important agent in the treatment of patients with stable angina. Low-dose aspirin is recommended for chronic stable angina and ischemic heart disease in all patients except those who have contraindication with the aspirin treatment\textsuperscript{106}.

4.7.3. Stroke

Stroke is the important cause of morbidity and mortality worldwide and antiplatelet agents are necessary for secondary stroke prevention\textsuperscript{107,108}. Aspirin is found to be very effective therapy for the secondary prevention of stroke in patients with ischemic stroke or transient ischemic attack\textsuperscript{109}. Antiplatelet agent and statins has been found very effective to reduce the risk of recurrent stroke and other vascular events\textsuperscript{110,111}. Aspirin found to be very cost effective and in 100 mg daily dose, it reduce the risk of MIs and stroke about 30\%\textsuperscript{112}. Combination of clopidogrel and aspirin has been found to be very effective in reducing the risk of hemorrhage up to 30\% specifically in Chinese patients with Transient ischemic attack (TIA) or minor stroke if treated within 24 hours after the onset of symptoms as compared to aspirin alone\textsuperscript{113}. However in some cases fatal hemorrhages may occur although showed relative benefit in stroke incidence. The dual therapy showed 23\% reduction in ischemic stroke but among these patients there is also 12\% non-significant increase in intra-cerebral haemorrhages\textsuperscript{114}. A meta-analysis of randomized control trials have been shown aspirin therapy is beneficial for secondary prophylaxis and found greater benefit as compared to their risk balance\textsuperscript{115}. In patients who have contraindication with warfarin treatment, aspirin with clopidogrel is found to be as an alternative preventive therapy recommended by guidelines for atrial fibrillation\textsuperscript{116}. It was also recommended by American College of Chest Physicians guideline (2012) that aspirin in combination with dipyridamole was found to be very effective for secondary prevention of stroke as compared to aspirin or clopidogrel alone\textsuperscript{114}. Aspirin in combination with clopidogrel or with dipyridamole are the good alternatives after ischemic stroke or transient ischemic stroke and this treatment continued to life time\textsuperscript{117}.

5. CONCLUSION

Aspirin is the most widely used analgesic drug which has also found use in many other diseases including cancer, Kawasaki disease, migraine, diabetes, pre-eclampsia and cardiovascular disease. It has shown good pharmacological activity against various pathological conditions associated with these diseases with minimum side effects. However, further clinical studies against other diseased conditions are being conducted which would help in better understanding of the use and action of this drug especially in combination therapy.

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