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Review article

Aspirin in a new role in human body

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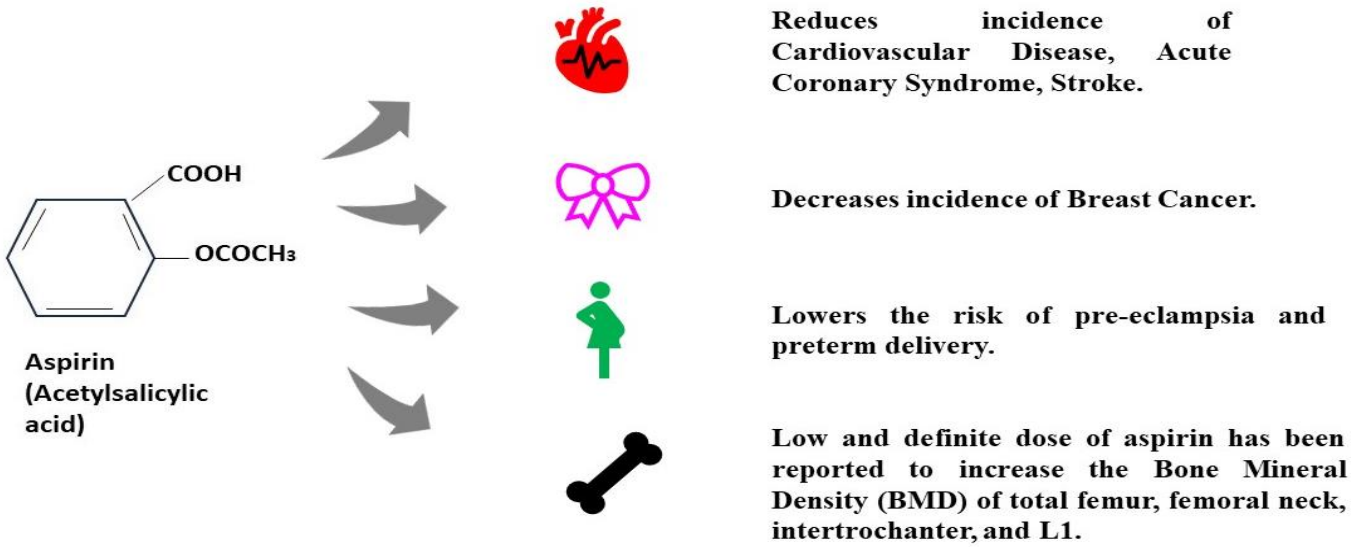
ABSTRACT

In 1897, German chemist Felix Hoffman synthesized acetylsalicylic acid, known as aspirin, which revolutionized its widespread modern use for pain relief. Aspirin acts as an inhibitor of cyclooxygenase-1 (COX-1) and has a modifying effect on the enzymatic activity of cyclooxygenase-2 (COX-2). It inhibits the production of prostaglandins, crucial for various physiological processes, and has been linked to a reduced risk of pre-eclampsia and preterm delivery before 34 weeks of pregnancy. However, aspirin's COX-1 inhibition is irreversible and long-lasting, requiring new enzymes to replace those acetylated. Low-dose aspirin has been reported to increase bone mineral density (BMD) in elderly individuals, coinciding with the growing prevalence of osteoporosis. However, a definitive connection between the use of low-dose aspirin and BMD remains elusive. A study examined the relationship between low-dose aspirin use and BMD in adults aged 50 to 80. A higher BMD in the femur, intertrochanter, and L1 regions compared to those who do not use aspirin was reported. However, the abstract acknowledges limitations and emphasizes the need for future research, including randomized controlled trials, to establish a causal relationship between low-dose aspirin use and enhanced bone density.

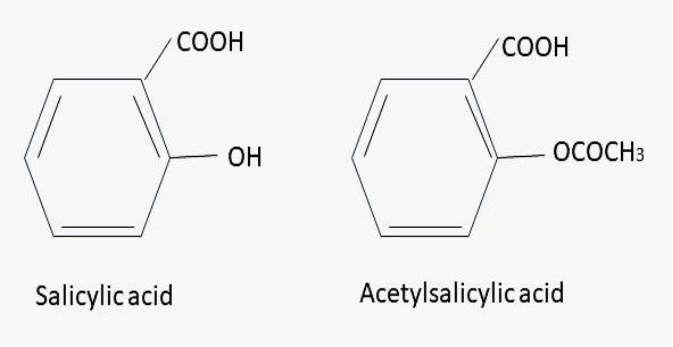


Keywords: Aspirin, COX-1, COX-2, Osteoporosis, Bone mineral density.

INTRODUCTION

In 1897, German chemist Felix Hoffman, employed by Bayer, synthesized acetylsalicylic acid, known as aspirin (Fig. 1). Coming year, Heinrich Dreser at Bayer disregarded its potential due to concerns about its impact on the heart. However, his primary focus was on promoting another new drug, heroin [1]. Arthur Eichengruen, responsible for innovative products at Bayer, persisted in advocating for acetylsalicylic acid's development. Eventually, Dreser examined aspirin on himself and rabbits, reassuring its curative value and improved stomach tolerance compared to salicylic acid [2]. Felix Hoffmann's innovation revolutionized aspirin's widespread modern use for pain relief.

Figure1: Aspirin, also known as acetylsalicylic acid



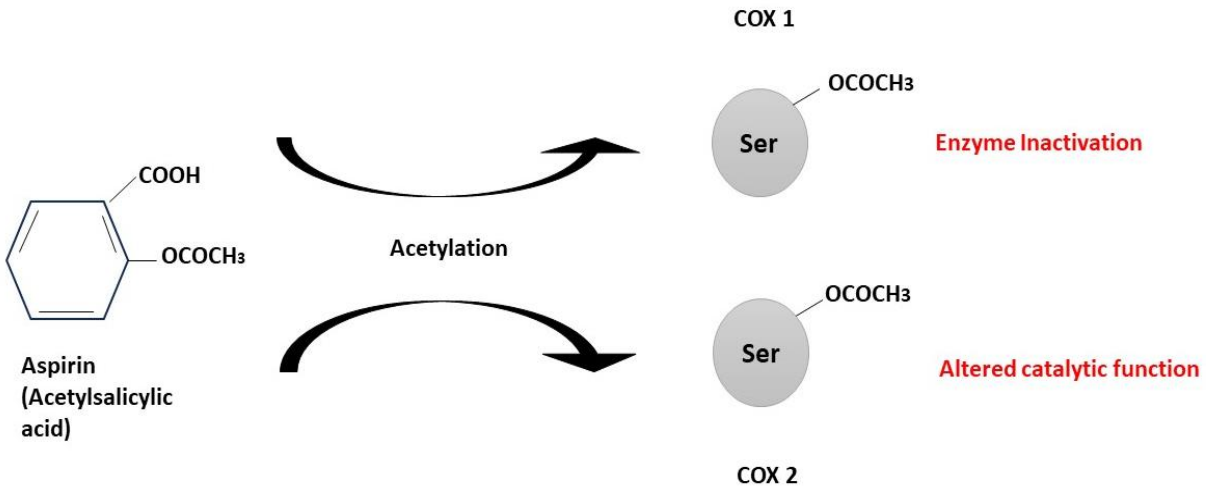
Maintains the carboxyl group (COOH) of salicylic acid while replacing the hydroxyl group (OH). This innovative drug was created by Felix Hoffmann at Bayer.

Mechanism of action of aspirin

Aspirin acts as an inhibitor of COX-1 and has a modifying effect on the enzymatic activity of COX-2 [3]. In contrast to other non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and naproxen, which bind to the enzyme reversibly, aspirin's binding is irreversible [4]. Aspirin also irreversibly inhibits thromboxane A2 on platelets, preventing their aggregation [5, 6]. Scientists postulate that when the COX pathway is blocked, arachidonic acids are redirected toward the lipoxygenase pathway. This redirection leads to the creation of anti-inflammatory lipoxins by altering prostaglandin-endoperoxide synthase (PTGS2), also known as COX-2. These modified compounds, mainly anti-inflammatory in nature, are referred to as aspirin-triggered lipoxins, resolvins, and maresins [7].

Aspirin inhibits the cyclooxygenase (COX) pathway, specifically COX-1 and COX-2 enzymes, which produce prostaglandins, crucial for various physiological processes. Aspirin, acetylsalicylic acid, irreversibly acetylates these enzymes, preventing their activity and reducing their production (Fig.2). This results in an anti-inflammatory effect, analgesic effect, antipyretic effect, and antiplatelet effect. Aspirin's inhibition of COX-1 in platelets suppresses the formation of thromboxane A2, a prostaglandin that promotes platelet aggregation and blood clotting. This antiplatelet effect is often prescribed for preventing heart attacks and strokes. However, aspirin's COX-1 inhibition is irreversible and long-lasting, requiring new enzymes to replace those acetylated. It should be used under medical guidance, especially in long-term or high-dose regimens.

Figure 2: The mechanism of action of aspirin involves the acetylation of cyclooxygenase (COX).



Aspirin adds an acetyl group to a serine (Ser) residue of COX, leading to the irreversible inactivation of COX-1. In the case of COX-2, aspirin inhibits its ability to produce prostaglandins while simultaneously triggering the generation of new protective lipid mediators.

Non-canonical function of aspirin

Alghamdi et al. 2007, conducted a study involving 1,748 participants, with 913 in the aspirin group and 835 in the control group. Their findings indicated that aspirin use was analogous with an enhancement in blood loss, transfusions of red cells, and fresh frozen plasma transfusions in bypass graft patients. However, there was no observed impact on platelet transfusions [8].

Similarly, Askie et al. 2007, conducted a study involving 32,217 women and 32,819 babies. Their research demonstrated that the use of aspirin lowered the risk of pre-eclampsia and preterm delivery before 34 weeks of pregnancy. However, it did not show any significant effects on maternal or fetal outcomes [9]. Bujold et al. also conducted an experiment, the results of which aligned with the findings mentioned earlier. Their study revealed that aspirin therapy that commenced before 16 weeks of pregnancy was linked with a lower incidence of pre-eclampsia, severe pre-eclampsia, and gestational hypertension [10]. Another significant study in 2009 involved 95,000 participants to investigate aspirin's role as a primary preventive agent against cardiovascular diseases and stroke leading to death. Additionally, it involved 17,000 participants to examine aspirin as a secondary preventive agent for these conditions.

Aspirin therapy as a primary preventive measure resulted in a notable depletion in serious vascular events and non-fatal myocardial infarction, but it did not affect the incidence of stroke or vascular mortality. In contrast, the secondary prevention with aspirin significantly reduced serious vascular events, strokes, and coronary events. However, a significant escalation in extracranial bleeding was linked to this [11]. Berger et al. conducted a study in 2009, which reported that aspirin therapy was associated with a significant scaling down of the incidence of non-fatal stroke. However, it did not impact all-cause mortality or myocardial infarction [12]. Cole et al. (2009) found in their work that there was a reduction in the frequency of occurrence of adenomas and advanced lesions associated with aspirin therapy when compared to the placebo group [13]. In 2008, a study involving 236,655 participants revealed that aspirin therapy was statistically associated with a reduction in the occurrence of breast cancer [14]. Two additional studies, one from 2008 by Kraspoulos and another from 2009 by De Berardis et al., aimed to assess the efficacy of aspirin in cardiovascular disease. Kraspoulos' study suggested that there was a significantly increased risk of cardiovascular events, death, and acute coronary syndrome among aspirin-resistant patients [14]. However, De Berardis et al. found that in diabetes patient's aspirin therapy was not significantly associated with a lowering in cardiovascular events, cardiovascular mortality, or overall mortality [15].

In a recent work published in scientific reports, which has been marked as one of the top 25 publications in Nature in the year 2022, a low and definite dose of aspirin has been reported to increase BMD [16]. The utilization of low-dose aspirin in elderly individuals is on the rise, coinciding with the growing prevalence of osteoporosis. Various research studies have investigated the efficacy of aspirin on bone metabolism. Nevertheless, a definitive connection between the use of low-dose aspirin and BMD remained elusive to date. BMD and structure in young rat models of osteoporosis were seen to improve in aspirin - therapy, but there is no conclusive evidence in human subjects. A study found a higher BMD in the hips and spine of women who took aspirin five to seven times a week compared to the ones who did not take aspirin. A study by Carbone et al. showed significant enhancement in systemic BMD among individuals using aspirin alone and in combination with some definite nonsteroidal anti-inflammatory drugs compared to COX2 inhibitors. However, this study included only two communities and a limited sample size. No randomized controlled trials have been conducted to explore the impact of aspirin treatment on human fracture risk and its connection with BMD remains inconclusive.

Osteoporosis is a bone metabolic condition where bone loss surpasses bone formation, leading to decreased bone mass, deterioration of bone tissue, increased fragility, and increased fracture susceptibility. Prostaglandin E2, a precursor to inflammatory molecules, plays a crucial role in bone metabolism. Aspirin, an NSAID, inhibits PGE2 synthesis by blocking COX activity, influencing bone metabolism. Aspirin's effects on bone density vary, with some resulting in increased bone mineral density, while others may increase nitric oxide production, reducing osteoblast activity and reducing bone mineral density [17].

The study examined the association between low-dose aspirin use and BMD in adults whose ages ranged between 50 to 80. It involved a cross-sectional examination of 15,560 participants between 2017 and March 2020 from the National Health and Nutrition Examination Survey (NHANES). A multivariate logistic regression model was used to assess the correlation between low-dose aspirin use and BMD at various skeletal sites. This cross-sectional study delved into the relationship between low-dose aspirin usage and various aspects of bone density, including total femur BMD, femoral neck BMD, intertrochanter BMD, and L1 BMD. In a nutshell, the findings predominantly revealed that low-dose aspirin users in the general U.S. population tend to exhibit significantly higher BMD in the total femur, intertrochanter, and L1 regions when compared to those who do not use aspirin. Notably, femoral neck BMD also showed a notable increase, particularly after accounting for multiple influencing factors.

Furthermore, detailed analyses considering different cohorts and sexes demonstrated that the influence of low-dose aspirin on bone mineral density remained consistent and did not exhibit significant variations. This study used a diverse, multiracial U.S. population sample for a comprehensive representation, accounting for potential confounding variables like heart attack history, physical activity, education, fractures, medications, smoking habits, serum creatinine, uric acid, and alcohol consumption to provide detailed subgroup analyses [18].

Limitations of the present work

The study of Liu, H., et al. 2022, comes with several limitations. Firstly, being cross-sectional in nature, it cannot track changes in BMD over time due to aspirin use, and it cannot establish a causal relationship. Secondly, the study lacks information regarding the duration and precise dosage of aspirin therapy, making it impossible to correlate the consequence of aspirin dose with BMD. Thirdly, the study only measured BMD and did not include other measures for assessing bone quality and microarchitecture, such as Computerized Tomography (CT) or bone turnover markers. Additionally, the study did not account for medications like thiazide diuretics and statins, which are known to influence BMD, despite adjusting for the presence of cardiovascular disease.

CONCLUSION

In summary, the findings suggest that low-dose aspirin may enhance bone mineral density across various cohorts and sex. However, given the cross-sectional design, future research should explore longitudinal changes in BMD among low-dose aspirin users. Furthermore, establishing a causal relationship would necessitate randomized controlled trials.

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