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Article

Effects of common supplements on human platelet aggregation in vitro

Nikhil Prabhakar[1], Anjana Prabhakar[1]
[1]Fremont High School, Sunnyvale, California

SUMMARY

Numerous factors can trigger platelet aggregation, and many compounds have been assessed for their ability to inhibit this process. However, conventional anti-platelet drugs have numerous side effects that warrant the development of alternative therapies. Considering the importance of platelets in thrombotic events and the economic burdens associated with cardiovascular disease (CVDs), exploring alternative therapies synergistic with conventional pharmacotherapies is paramount. In this study, we sought to investigate the role of dietary supplements on platelet aggregation. We hypothesized that common dietary supplements would act to prevent platelet aggregation in an in vitro assay. We examined supplements that had claims of general health benefits related to decreasing inflammation, a factor established as a risk factor for cardiovascular disease. We tested nicotinamide mononucleotide, ResveraCel, Meriva, berberine, and zinc. We treated human platelets with these five supplements and evaluated their ability to modulate platelet aggregation. Aggregates were defined by treating platelets with a positive control, phorbol 12-myristate 13-acetate, which is known to induce aggregation via the activation of surface adhesion molecules. The number of platelet aggregates was quantified using a hemocytometer and microscope. While some supplements promoted platelet aggregation, ResveraCel and berberine were found to reduce platelet aggregation. These results open the potential for a new understanding of the role nutritional supplementation may play in CVDs.

INTRODUCTION

Cardiovascular diseases (CVDs) are responsible for approximately 17.9 million deaths annually, constituting 31% of all global deaths (1). This epidemic imposes a significant economic burden, with CVDs projected to cost over $1.1 trillion US dollars in the United States alone by 2035 (1). Inquiry into platelet aggregation can offer insights into how we may disrupt blood clotting and potentially prevent CVDs. Platelet aggregation contributes to thrombotic events by providing the basis for the formation of blood clots, including those associated with heart attack and stroke (4). Inhibiting platelet aggregation would also prevent the formation of blood clots. This strategy has been successfully employed through the use of antiplatelet drugs, like clopidogrel, in individuals who are at risk for a CVD event (5). Clopidogrel saw approximately 16 million prescriptions in the United States in 2021 (6). The success of clopidogrel suggests that other compounds that inhibit platelet aggregation may be helpful in helping to prevent or lessen the severity of CVD events.

Federal Drug Administration-approved therapies, such as clopidogrel, are effective in treating CVDs like stroke and heart attack. However, their side effects can range from moderate issues like persistent nosebleeds to more severe symptoms, such as hemoptysis (coughing up blood) (7). The more severe symptoms may cause patients to discontinue their treatments, increasing their risks of suffering a thrombotic event (8). Antiplatelet drugs are the standard of care after an individual has had a thrombotic event to prevent recurrence, but they may also be prescribed to high-risk individuals to prevent initial CVD events. Another strategy for the prevention of first-time thrombotic events could involve low-risk, proactive treatment options such as nutritional supplements in addition to the standard of care.

The tremendous global morbidity and economic impact of CVDs underscores the need for more preventative strategies that are safe, efficacious, and that can be used with current therapeutics. Dietary supplements that reduce platelet aggregation may provide a synergistic effect with drugs like clopidogrel, helping to reduce the dose or duration needed by a patient and, thereby, reduce the likelihood of severe side effects. The supplements we tested are not without their own side effects, but the side effects of taking these supplements rarely lead to severe reactions. These supplements may provide one solution to managing CVD in patients who would otherwise stop taking drugs like clopidogrel due to the side effects. The supplements berberine, zinc, curcumin (Meriva), resveratrol (ResveraCel), and nicotinamide mononucleotide (NMN) have all previously been studied for their efficacy and safety (9–13). However, more research must be conducted into the effects of these supplements on platelet aggregation and their ability to act as mild platelet anti-aggregation agents.

We investigated the impact of common dietary supplements, specifically NMN, trans-resveratrol (ResveraCel), curcumin (Meriva), berberine, and zinc, in an in vitro platelet aggregation assay. ResveraCel's main component, trans-resveratrol, has previously been studied for its role in preventing platelet aggregation and inflammation associated with the blood vessels while NMN, Meriva, berberine, and zinc have mostly been studied for their anti-inflammatory properties (14,15).

Curcumin (Meriva) has antioxidant and anti-inflammatory qualities and is also reported to affect platelet activation (16). Inflammation affects platelet aggregation and thrombogenesis through pro-inflammatory cytokines. These cytokines upregulate platelet surface receptors and endothelial adhesion molecules, increasing platelet adhesion, activation, and aggregation (17). Inflammation also increases

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reactive oxygen species production, which activates potent platelet activators like thrombin and Von Willebrand factors, promoting pathways leading to platelet aggregation (18). In addition to Meriva, we chose zinc because prior research has identified its role in immune system maintenance and its ability to influence platelet aggregation via intracellular signaling pathways (19). Berberine has been reported to lower low-density lipoprotein cholesterol, helping to prevent atherosclerosis, reduce vascular inflammation, and in doing so, reduce platelet aggregation. Furthermore, berberine increases high-density lipoprotein cholesterol, which has anti-inflammatory properties (20). Berberine has also been reported to enhance insulin sensitivity and lower blood glucose levels, reducing hyperglycemia-induced platelet activation and aggregation (20). These positive effects on lipid profiles and glucose metabolism are known to inhibit platelet aggregation (21–23).

We hypothesized that the supplements NMN, ResveraCel, Meriva, berberine, and zinc could modulate in vitro platelet aggregation. We tested this by directly exposing human platelets to each of the five supplements in an in vitro assay and counting platelet aggregates using a light microscope. We found that both trans-resveratrol (ResveraCel) and berberine reduced platelet aggregation, while NMN, zinc, and curcumin (Meriva) caused platelet aggregation.

RESULTS

We studied the impact of five supplements, NMN, trans-resveratrol (ResveraCel), curcumin (Meriva), berberine, and zinc, on platelet aggregation. The supplements chosen were all orally formulated, and some contained active ingredients and inert chemicals to facilitate oral delivery. While ResveraCel contained 75 mg trans-resveratrol, the formulation also included inert hemicellulose and 125 mg quercetin—a flavonoid with strong antioxidant properties (24). Although the primary active compound in Meriva was curcumin, the curcumin was formulated within a lipid matrix to improve solubility. The zinc supplement was formulated as zinc picolinate, a zinc salt of picolinic acid. Berberine and NMN were pure and contained no other ingredients (**Table 1**).

To properly assess the effect of the tested supplements, a reliable control capable of inducing platelet aggregation at room temperature was necessary. We considered three controls potentially capable of inducing aggregation: phorbol 12-myristate 13-acetate (PMA), mechanical aggregation, and ethanol. Additionally, PBS was used as a vehicle control.

We tested platelets from a single donor with 6% ethanol, 0.07 mg/ml PMA, and mechanical stress in triplicate tubes. A final concentration of six percent ethanol, 0.07 mg/mL PMA, and ~2.5 x 10^6 platelets were incubated at room temperature for a minimum of 30 minutes before loading into the hemacytometer to manually count aggregates using a standard light microscope. Platelet aggregates were defined as platelet clumps having more than five platelets.

We found that PMA induced the most platelet aggregation with an average of 129 aggregates compared to platelets in PBS alone, which had an average of 21 aggregates ($p < 0.05$). Ethanol had a modest effect on platelet aggregation with an average of 31 aggregates but was not significant ($p = 0.052$) when compared to the platelets in PBS (**Figure 1**).

When considering controls that would induce platelet aggregation, we also hypothesized that simple mechanical stress may lead to aggregation since platelets can be activated under sheer stress conditions (25). We tested this hypothesis by subjecting platelets in PBS to vigorous pipetting with a standard micropipetter. Each sample of platelets was pipetted up and down rapidly for a total of 15 cycles; platelets were then incubated and counted as described previously. When compared to PMA-induced aggregation, the mechanical stimulation had fewer aggregates: an average of 59 aggregates compared to an average of 129 aggregates, respectively ($p < 0.01$) (**Figure 1**). Mechanical stimulation and 6% ethanol induced less aggregation compared to PMA. Based on these data, PMA was chosen as our positive control.

In addition to determining a reliable positive control, our assay required clear parameters on what qualified as a platelet aggregate. From our positive control determination study, we concluded that aggregates required a total of five or more platelets to be counted as a single aggregate. We observed many small platelet clusters that we believed did not represent true platelet aggregation. We made no effort to distinguish the size of the aggregates and counted them equally as one aggregation event (**Figure 2**).

Having established PMA as a positive control and having determined what qualified as a platelet aggregate, we then exposed the purified human platelets to each supplement. Supplement suspensions were added to tubes containing ~2.5 x 10^6 platelets in a total volume of 15 µL and were incubated for 30–60 minutes at room temperature. Each supplement was tested at a single concentration determined by the amount of active ingredient per pill and solubility. We used the following concentrations for each supplement: 6.3 mM zinc, 47 mM curcumin (Meriva), 50 mM NMN, 290 mM berberine, and 110 mM trans-resveratrol (ResveraCel). Additionally, each supplement was tested on two preparations of platelets from two separate donors in triplicate. ResveraCel, zinc, berberine, and NMN were suspended in PBS, while Meriva was dissolved in 95% ethanol for better solubility. While Meriva was suspended in ethanol, we observed no effect of

Dietary Supplement	Ingredients in one capsule
ResveraCel	75 mg trans-resveratrol, 207.5 mg nicotinamide riboside hydrogen malate, 125 mg quercetin phytosome ((Sophora japonica) extract (flower) / phospholipid complex from sunflower), 42.5 mg betaine anhydrous (trimethylglycine)
NMN	250 mg beta-nicotinamide mononucleotide (NMN)
Berberine	480 mg goldenseal berberine (hydrastis canadensis L. (root))
Meriva	250 mg curcumin phytosome (curcuma longa extract (root) / phospholipid complex from sunflower)
Zinc	30 mg zinc picolinate

Table 1: Ingredients of the dietary supplements. Listed are the supplements tested on platelet aggregation and the complete list of ingredients in a single capsule.

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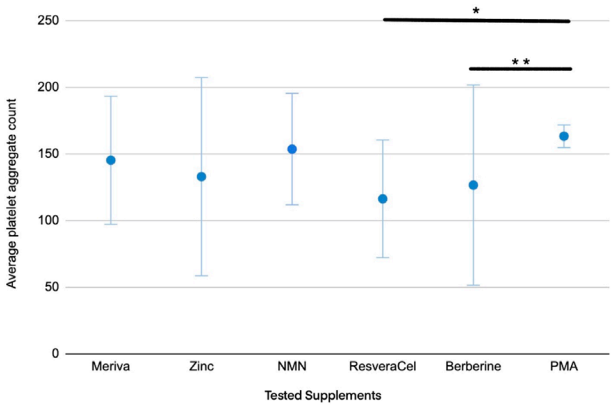

Figure 1: Quantification of platelet aggregation in response to chemical and mechanical stimulation. Platelets were exposed to 0.07 mg/ml PMA, mechanical stress, 6% ethanol, and PBS to determine the effects each had on platelet aggregation. Each point represents the average number of platelet aggregates per condition. Error bars represent SD, n = 2. PMA compared to the PBS (***p < 0.01) and mechanical aggregation compared to the PBS (**p < 0.01) were statistically significant. 6% ethanol compared to the PBS was not significant (p = 0.052). Each sample was incubated for 30 minutes at 25°C.

ethanol alone on platelet aggregation in our initial study.

We found differing platelet aggregation in response to the supplements. Zinc, Meriva, and NMN all caused platelet aggregation. Zinc at 6.3 mM resulted in an average of 133 aggregates, while 47 mM Meriva and 50 mM NMN averaged 145 and 154 aggregates, respectively. We found that these data were not significantly different from the PMA positive control, which had an average of 164 aggregates (p-value for Meriva = 0.0617, zinc = 0.135, NMN = 0.138, **Figure 3**).

We found that, in contrast to the other supplements, berberine and ResveraCel had less platelet aggregation than the PMA control. Berberine, at a concentration of 290 mM, resulted in an average of 127 aggregates, which was significantly lower than PMA ($p < 0.05$). Additionally, ResveraCel, at a concentration of 110 mM, averaged 116 aggregates, which was also significantly less than PMA ($p < 0.01$, **Figure 3**).

DISCUSSION

The persistent global challenge of preventing and treating CVD underscores the need for exploring alternative therapeutic strategies to enhance current treatments. One such option is the potential for reducing platelet aggregation through dietary supplementation. We investigated five supplements due to their purported ability to directly or indirectly influence platelet aggregation, a critical factor in the pathogenesis of cardiovascular diseases. We hypothesized that common dietary supplements could be used to modulate platelet aggregation and provide an additional therapeutic option for patients being treated for CVD. We used human platelets from separate donors to test five common supplements, Meriva, ResveraCel, berberine, zinc, and NMN, in an in vitro platelet aggregation assay. We found that, while NMN, zinc, and Meriva induced platelet aggregation, ResveraCel and berberine significantly limited the number of aggregates compared to the PMA positive control. Our data suggests that ResveraCel and berberine warrant further study.

We found that ResveraCel significantly reduced platelet aggregation in our in vitro assay. However, our data was complicated by confounding factors. ResveraCel is formulated for oral administration with inert ingredients like hemicellulose and contains other active compounds, including quercetin, betaine, and nicotinamide riboside. Therefore, we cannot fully ascribe our results with ResveraCel to the direct action of trans-resveratrol. Additionally, our assay is limited to the detection of compounds and conditions that have a direct effect on platelet aggregation and cannot be used to assess indirect effects. While platelet aggregation can be induced through inflammation and oxidative stress, and trans-resveratrol is recognized for its antioxidant and anti-inflammatory properties, our assay cannot be used to measure these complex physiologies and their perturbation (26, 27). These factors underscore the need for further research using purified compounds and testing done under more physiologically relevant conditions.

In addition to the effects of ResveraCel on platelet aggregation, we also found that berberine reduced platelet aggregation. Unlike ResveraCel, the berberine formulation had no other active ingredients to confound the results. Berberine has been reported to have a direct effect on platelets through the inhibition of intracellular enzymes and signaling molecules involved in platelet activation (28, 29). Our results may reflect this inhibition. Berberine may be acting directly upon the platelets in our assay, inhibiting cytosolic pathways preventing activation and subsequent aggregation. We would need to conduct further analysis of berberine's effect on platelet aggregation to determine which, if any, of these pathways may be affected.

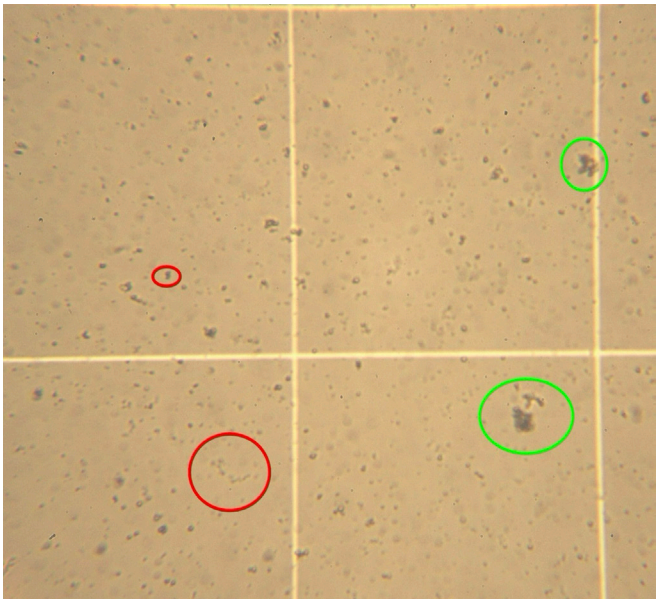

Figure 2: Representative platelet aggregates. Platelet aggregates were defined by microscopy of a count that included 5 or more platelets. Green circles represent counted platelet aggregates while red circles represent clumps of platelets that we deemed too small to be considered aggregates. Samples were examined using micrographs taken at 100x magnification.

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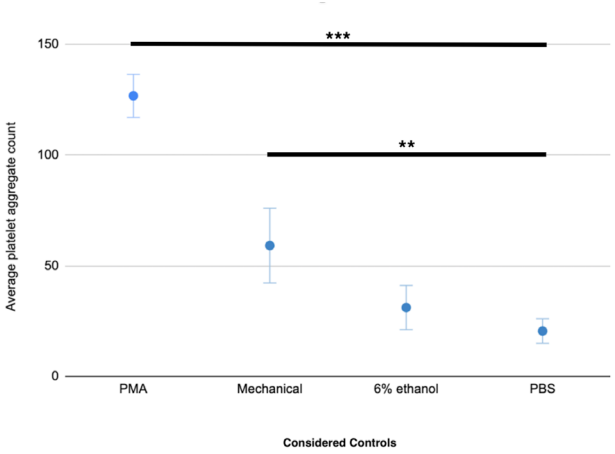

Figure 3: Average platelet aggregate count in response to tested supplements. Platelets aggregates were counted and averaged for each supplement condition, n = 3, error bars = SD. The following supplements showed statistically significantly different average aggregation: ResveraCel and PMA, *p < 0.01; Berberine and PMA, **p < 0.05. These supplements were not statistically significant when compared to PMA: Meriva, p = 0.0617; Zinc, p = 0.135; NMN, p = 0.138.

We predicted that the supplements tested would reduce platelet aggregation, but we found that Meriva, NMN, and zinc did not reduce aggregation. However, these supplements did increase aggregation. These data contradict observations about curcumin, the main compound in Meriva, demonstrating it has the ability to inhibit platelet aggregation by preventing calcium signaling (30). This mechanism relies on the activation of proteins that circulate in the blood. Our assay, having used washed platelets, may not test this interaction and thus curcumin may not have been able to inhibit platelet aggregation through this pathway in our assay. Adding serum to our platelets or conducting a similar type of assay in whole blood may be a better strategy for future analysis of the effects of curcumin as an antiplatelet supplement.

We also recognize the need to establish vehicle controls for many of the supplements. Oral formulation of the supplements often includes carriers like hemicellulose and other binders. We do not know what effects these compounds may have on platelets without testing them independently. Additionally, Meriva is a formulation of curcumin suspended in phospholipids. Cellular phospholipids are known to activate platelets, so we cannot establish a clear effect for curcumin in the presence of phospholipids without first knowing if the phospholipids have their own effect on the platelets (31).

Moreover, the use of a purified, washed platelet suspension in PBS, rather than whole blood, presents another limitation. The absence of the complex interactions that occur in the bloodstream, including the presence of other cells, plasma proteins, and molecular factors, may have influenced the results. Additionally, we conducted our experiments at room temperature, which deviates from the physiological body temperature at which enzymatic and biochemical reactions, including those involving platelet function, occur more optimally.

We hypothesized that common supplements could modulate platelet activation and prevent aggregation. We used an in vitro assay to test the direct effects of ResveraCel, Meriva, zinc, berberine, and NMN on platelet aggregation. Our results showed that ResveraCel and berberine acted to reduce platelet aggregation while Meriva, zinc, and NMN did not. However, confounding factors including, but not limited to, the complex formulations of the supplements, the limitations of the platelet aggregation assay in assessing more complex biology, and need for individual vehicle controls prevent us from getting a clearer understanding of the role these supplements may be playing in modulating platelet aggregation. Despite these limitations, we gained new insights into the role supplements may play in modulating platelet aggregation.

MATERIALS AND METHODS

Platelet Aggregation Assay

We began by selecting and purchasing common dietary supplements. These were ResveraCel (Thorne), Meriva (Thorne), zinc picolinate (Thorne), berberine (PURE), and NMN (Maac10). Stock solutions for each supplement were prepared by dissolving the contents of one capsule in 5 mL of phosphate buffer saline (PBS) (Albert Bio), with the exception of Meriva, which we dissolved in 95% ethanol (Carolina Biological) to increase solubility. The resulting concentrations were 50 mg/mL (0.15 M) NMN, 90 mg/mL (0.33 M) ResveraCel, 6 mg/mL (0.019 M) zinc, 50 mg/mL (0.14 M) Meriva, and 96 mg/mL (0.29 M) berberine.

Human platelets purchased from HumanCells Biosciences at a concentration of 250 million platelets per mL were suspended in 20 mL PBS kept at 20° C. A total of three separate platelet donors were used in the assays. One donor's platelets were used to establish the control that would cause platelet aggregation, while the other two donors' platelets were used in the supplement testing assays. Separate platelet donors were used to carry out the assays on separate days. Time constraints limited the number of platelet aggregations that could be counted in one day, causing the use of multiple donors for separate assays.

In establishing the positive control, we considered mechanical aggregation, ethanol, and PMA. PBS was used as a negative control. For mechanical aggregation, ~2.5 x 10^6 platelets were agitated using vigorous pipetting for a total of 15 cycles. For ethanol, 1 µL 95% ethanol was added to 10 µL of the platelet suspension (~ 2.5 x 10^6 total platelets), then PBS was used to bring the volume up to 15 µL, for a final concentration of 6% ethanol. PMA at 1 µg/uL was loaded similarly to ethanol, with 1 µL PMA and 4 µL PBS added to a 10 µL platelet suspension for a final concentration of 0.07 mg/mL PMA. Platelets were then incubated for 30-60 minutes at room temperature, before loading 10 µL of each preparation into a hemacytometer (Neubauer) and the platelet aggregates were then counted using 100x magnification using a compound light microscope (SWIFT). This initial aggregation assay was run for a total of two trials using two different platelet donors.

To prepare the supplement aggregate assay, 5 µL of each supplement stock solution was added to 10 µL of platelets. For the positive control, 1 µL of PMA was added to the 10 µL of platelets, and the final volume was brought to 15 µL using PBS. All preparations were incubated at room temperature for 30 minutes. After incubation, 10 µL of each preparation and platelet aggregates were counted as described previously. This assay was run for a total of three trials.

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Statistical Analysis

p-values were calculated using the PBS control or by comparing the data from the supplements with the positive PMA control using Student's t-test (two-tailed). Calculated p-values < 0.05 were considered statistically significant.

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