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Pharmacology and toxicology

Effect of a diet rich in potato peel on platelet aggregation

Efecto de una dieta rica en cáscara de papa sobre la agregación plaquetaria

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Abstract

Background: Potato peel extract has demonstrated the ability to reduce platelet aggregation *in vitro*, suggesting its potential as a dietary intervention for preventing atherothrombotic disorders.

Objective: This study aims to evaluate the impact of a potato peel-rich diet on platelet aggregation.

Methods: A randomized, crossover-controlled, open two-period study was carried out with the participation of 12 healthy volunteers. Platelet aggregation was assessed before and after a seven-day dietary intervention. Participants consumed either a diet rich in potato peel (2 g/kg/d) or acetylsalicylic acid (ASA) as a reference (100 mg/d). Platelet aggregation percentages were measured following stimulation with arachidonic acid (AA, 150 µg/mL), adenosine diphosphate (ADP, 10 µM), and collagen (COL, 10 µg/mL).

Results: The potato peel-rich diet resulted in a slight but significant reduction in platelet aggregation when stimulated with arachidonic acid compared to baseline values (85.0±2.0% vs. 91.3±1.7%, $p<0.05$). This effect was less pronounced than the reduction achieved with ASA (16±1.9%, $p<0.001$).

Conclusion: The administration of a diet rich in potato peel reduces platelet aggregation induced by arachidonic acid, suggesting its potential role in the prevention of atherothrombotic disorders.

Keywords: *Solanum tuberosum*, Potato, Platelet aggregation, Caffeic acid, Chlorogenic acid.

Resumen

Introducción: El extracto de cáscara de patata ha demostrado su capacidad para reducir la agregación plaquetaria in vitro, lo que sugiere su potencial como intervención dietética para prevenir trastornos aterotrombóticos.

Objetivo: Evaluar el impacto de una dieta rica en cáscara de patata en la agregación plaquetaria.

Materiales y métodos: Se llevó a cabo un estudio aleatorizado, controlado, cruzado y abierto con la participación de 12 voluntarios sanos. Se evaluó la agregación

plaquetaria antes y después de una intervención dietética de siete días. Los participantes consumieron una dieta rica en cáscara de patata (2 g/kg/d) o ácido acetilsalicílico (ASA) como referente (100 mg/d). Se midieron los porcentajes de agregación plaquetaria después de la estimulación con ácido araquidónico (AA, 150 µg/mL), difosfato de adenosina (ADP, 10 µM) y colágeno (COL, 10 µg/mL).
Resultados:
La dieta rica en cáscara de patata resultó en una ligera pero significativa reducción en la agregación plaquetaria cuando se estimuló con ácido araquidónico en comparación con los valores iniciales (85,0 ± 2,0% vs. 91,3 ± 1,7%, $p < 0{,}05$). Este efecto fue menos pronunciado que la reducción lograda con ASA (16 ± 1,9%, $p < 0{,}001$).
Conclusión: La administración de una dieta rica en cáscara de patata reduce la agregación plaquetaria inducida por ácido araquidónico, lo que sugiere su papel potencial en la prevención de trastornos aterotrombóticos.
Palabras clave: *Solanum tuberosum*, papa, agregación plaquetaria, ácido caféico, ácido clorogénico.

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Introduction

Adequate nutrition, along with regular exercise and healthy lifestyle habits, plays a pivotal role in preventing atherothrombotic diseases. Mediterranean diets and the consumption of omega-3 polyunsaturated fatty acids (PUFAs) are inversely associated with cardiovascular diseases (CVD). Furthermore, certain nutrients, particularly those rich in polyphenols, show promise in preventing CVD. A significant aspect of their efficacy appears to lie in their ability to inhibit platelet activation and aggregation, thus reducing the risk of thrombus formation [1]. Nevertheless, while nutrition is indeed critical, individual genetics, underlying health conditions, and various other factors collectively contribute to one's overall risk of developing CVD.

Despite the advancements in pharmacological therapies and interventions, global public health concerns persist regarding the management of atherothrombotic diseases, which include interventions like stents and revascularization procedures. While the antiplatelet approach is crucial in managing complications, preventive and non-pharmacological interventions that support platelet function should be of paramount importance [2]. As a result, a synergistic blend of medical interventions and lifestyle adjustments remains essential in addressing atherothrombotic conditions and mitigating their impact on public health.

Given these considerations, the exploration of dietary sources with potential protective factors against cardiovascular diseases (CVD) has gained increasing relevance. While pharmacological strategies have emerged for the primary prevention of atherothrombotic disorders, especially in reducing complications like coronary artery disease, infarction, and stroke, the use of acetylsalicylic acid presents a delicate balance between efficacy and safety for primary prevention, particularly regarding the risk of bleeding [3]. Statins are recognized by regulatory agencies for primary prevention; however, concerns arise due to long-term side effects, costs, and inconveniences. In the face of these uncertainties, the importance of non-pharmacological measures cannot be overstated (3).

The identification of certain nutrients as potential protective factors against CVD adds a compelling dimension to the realm of diet-based preventive measures (4). While pharmacological approaches remain relevant, they come with inherent risks, emphasizing the significance of non-pharmacological measures, including lifestyle modifications. These non-pharmacological interventions are essential components of primary prevention due to their safety and holistic benefits.

Solanum tuberosum, commonly referred to as "papa," constitutes a staple in traditional diets in Colombia and other Andean regions. These tubers are rich in constituents such as caffeic acid and chlorogenic acid, which, along with the whole extract, have demonstrated antiplatelet properties in vitro. However, the role of *S. tuberosum* as a dietary preventive factor against cardiovascular disease remains to be established (5).

While these metabolites, along with the whole extract, exhibit antiplatelet properties *in vitro*, the potential of *S. tuberosum* as a dietary preventive factor against cardiovascular disease remains unconfirmed (5). *In vitro* studies suggest antiplatelet attributes, but further research is necessary to determine the actual impact of incorporating *S. tuberosum* into human diets to prevent cardiovascular disease.

At the core of platelet adhesion and aggregation is cyclooxygenase-1 (COX-1), a key enzyme responsible for catalyzing the production of thromboxane A2 (TxA2) from arachidonic acid (AA) (6). Therefore, strategies that target this pathway show promise in mitigating atherothrombotic disorders. Notably, *S. tuberosum* demonstrates antiplatelet properties, particularly in inhibiting the AA pathway, underscoring its potential for preventing thrombus formation (5).

However, the detailed mechanisms underlying these effects are not yet fully understood, highlighting the necessity for human studies to substantiate the role of *S. tuberosum* in preventing cardiovascular diseases.

Furthermore, the content of toxic glycoalkaloids solanine and solanidine in fresh potato tubers is minimal and lacks the antiplatelet properties associated with the species. This alleviates concerns about consuming a diet rich in potato peels (7, 8). As a result, moderate consumption of fresh potatoes, including their peels, is generally safe for most individuals, with consideration for potential sensitivities and allergies.

The potential benefits of a diet rich in potato skin in atheromatous disorders remain relatively unexplored. In addition to its nutritional value, the high fiber and antioxidant-rich nature of potato peel contribute to regular bowel function, reduced disease risk, and the mitigation of oxidative processes (9, 10). Notably, chlorogenic acid and caffeic acid, polyphenols found in S. tuberosum peels, exhibit antiplatelet properties that may be linked to their antioxidant effects (5, 11, 12). Since platelet aggregation plays a crucial role in atheromatous diseases, a diet rich in these antiplatelet metabolites holds promise in reducing the risk of coronary disease.

This study aims to investigate the impact of a potato peel-rich diet on platelet aggregation in healthy volunteers, with the goal of shedding light on its potential role in preventing prothrombotic artery disorders. By examining the influence of potato peel consumption on platelet function and cardiovascular health, this research contributes to the understanding of dietary strategies for reducing the risk of clot-related disorders.

Methods and materials

Diet preparation:

Approximately 60 kg of "pastusa" variety of *S. tuberosum* tubers were sourced from the locality of "El Manzano" (Ventaquemada municipality, Boyacá department, Colombia; coordinates 5° 21’ 59’’N, 73° 31’ 19’’W), adhering to Colombian technical standards for product acquisition. A plant specimen was submitted to the "Herbario Nacional Colombiano" (code COL-611951) to verify its botanical classification.

Peel preparation:

Fresh tuber peels were thoroughly washed and boiled for approximately 30 minutes, then sliced into 3 mm thick fragments. These peel fragments were administered at a ratio of 2 g per kg of body weight to each volunteer, once daily, over the course of one week under fasting conditions. This quantity is well below the toxic threshold for human consumption, considering that the average tuber contains 12-20 mg/kg of glycoalkaloids, while the toxic dose of glycoalkaloids ranges from 2 to 5 mg/kg [13, 14].

Outcomes:

The primary outcome measured the percentage decrease in platelet aggregation, assessed through light transmission aggregometry after seven days of administering a potato peel-rich diet. The platelet aggregation was induced using arachidonic acid (AA, 150 µg/mL), adenosine diphosphate (ADP, 10 µM), and collagen (COL, 10 µg/mL) as pro-aggregating agents [15-16]. A reference group received acetylsalicylic acid (ASA) (100 mg/d). Additionally, any treatment-related events were recorded.

Study design:

We conducted an open-label, randomized, single-dose, two-period, two-sequence, two-treatment crossover study involving 12 healthy volunteers. The sample size was selected based on the considerations for phase 1 studies, which typically involve a low number of patients and do not require a formal sample size calculation. Subjects were randomly assigned to receive a diet rich in potato peel (2 kg/kg/day) and ASA (100 mg/day) under fasting conditions, with a one-week washout period between treatments. Each treatment period spanned seven days.

Eligibility:

Eligible volunteers included men and women aged 18-45, weighing 50-80 kg, with a body mass index (BMI) of 18-30 kg/m². Participants were not on systemic medication, except for oral contraceptive pills. Individuals with contraindications to ASA or a medical history indicating an increased risk of bleeding were excluded. Volunteers adhered to a potato peel-rich diet, refrained from caffeine consumption and intense exercise the day before and during the study, and fasted overnight before study visits.

Platelet aggregation assays:

An 18 mL sample of whole blood was collected in vacuum tubes containing 3.2% sodium citrate as an anticoagulant at a 9:1 ratio. After 1 hour, the samples were centrifuged at 1000 rpm for 5 minutes to obtain platelet-rich plasma supernatant (PRP), which was stored at 37°C and used within 30 minutes. Blood was then further centrifuged for 10 minutes at 3500 rpm to obtain platelet-poor plasma (PPP).

Aggregometer procedure:

In each channel of the AggRAM 1486 aggregometer (Helena Laboratories), we dispensed 450 µL of platelet-rich plasma (PRP) and incubated it for 5 minutes at 37°C after adding 50 µL of the platelet aggregation inducer: adenosine diphosphate (ADP; 10 µM), collagen (COLL; 10 µg/mL), or arachidonic acid (AA; 150 µg/mL). The tests were conducted using PRP samples collected from volunteers under baseline conditions (prior to treatment) and after treatment with ASA (100 mg/d for 7 days) or potato peel (2 g/kg/d for 7 days).
The data were expressed as a percentage of platelet aggregation based on transmittance values obtained from the aggregometer, with PRP representing 100% aggregation and PPP representing 0%.

Plaguicide trace analysis:

To eliminate the possibility of pesticide residue interference with the platelet aggregation test (17), a trace analysis of a potato peel sample was conducted at the Department of Chemistry, National University of Colombia in Bogotá, using the QuEChERS method (sample reference: m2043).

Data analysis:

A self-controlled crossover study was selected to ensure statistically valid results with a limited number of participants. This study involved 12 volunteers, resulting in two groups of 24 data points for each intervention (18-19).

Treatment assignment and timing:

Initially, individuals were randomly assigned to receive either the diet or ASA treatment. The timing for switching treatments was determined based on the average platelet lifespan of seven days, with a one-week washout period considered adequate. Given the brief elimination half-life of low-dose ASA (approximately 2-3 hours), platelet function should be fully recovered in period II (after the crossover).

Antiplatelet effect evaluation:

The assessment of the antiplatelet effect involved comparing platelet aggregation percentages before and after treatment. Data analysis included one-way repeated measure ANOVA followed by the Tukey multiple comparisons test. In cases where the parametric test assumptions were not met, a Friedman test was applied, followed by Dunn's multiple tests. Data analysis was conducted using GraphPad Prism version 6.05, with a significance level set at $p < 0.05$.

Drugs and chemicals:

The study employed the following reagents and drugs: ADP, COLL, and AA from Helena, and DMSO from Sigma-Aldrich. ASA, also from Sigma-Aldrich, was used as well. The confirmation of the S. tuberosum species was conducted through a comparison at the National University of Colombia (code COL-611951).

Ethical considerations:

This study adhered to the scientific, technical, and administrative standards for health research as outlined in Resolution 8430 of 1993 by the Ministry of Health in Colombia. Following articles 11 and 55, the study falls under the category of "minimal risk" as it involved the collection of blood by venipuncture in healthy adults and the administration of ASA (100 mg/d/7d), a widely used medication with a well-established safety profile and a broad therapeutic index. All volunteers provided written informed consent after meeting eligibility criteria. The study protocols were approved by the Ethics Committee of the Faculty of Sciences at Universidad Nacional de Colombia (Act 03/2019).

Results

During the period from May 6 to May 31, 2019, a total of 12 volunteers underwent randomization. In the initial phase (period I), six participants were allocated to a potato peel diet, while the remaining six were assigned to receive ASA. For the subsequent phase (period II), the interventions were switched. Detailed baseline characteristics of the volunteers are presented in Table 1. No adverse effects were reported that necessitated the discontinuation of the study.

Table 1. Characteristics of the Volunteers at Baseline*

Characteristics	Diet	ASA
N	6	6
Age - yr	23.2±3.1	23.5±3.1
Sex		
Male	3	2
Female	3	4
Weight - kg	58.7±7.1	58.6±6.6
Body-mass index	21.0±1.1	20.3±2.0
Basal platelet aggregation (%)	90.6±5.9	92.7±5.9

*At the start of period I (1 week), values are presented as means ± standard deviation (SD). During period II, volunteers received either the potato peel diet or acetylsalicylic acid (ASA) treatments in a crossover design.

The effect of a diet rich in potato peel on platelet aggregation was assessed by analyzing changes in aggregation percentages compared to baseline values among the participants. Following a seven-day administration of the potato peel-rich diet, a statistically significant decrease in platelet aggregation was observed when arachidonic acid (AA) was used as the stimulant (mean ± s.e.m: 91.85±1.75% to 85.02±2.0%, $p<0.05$) (as shown in Figure 1). While there was a trend towards reduced aggregation with ADP and COL as stimulants (91.2±1.8% to 83.7±2.39 for ADP, 92.1±2.3 to 89.4±2.0 for COL), this reduction did not reach statistical significance (see Figure 2 and Figure 3). Notably, acetylsalicylic acid (ASA) exhibited a suppressive effect on aggregation percentages for all three agonists, with the most significant impact observed against AA (16±1.98%) compared to ADP (66.0±4.7%) and COL (66.8±5.6%) (as depicted in Figures 1-3).

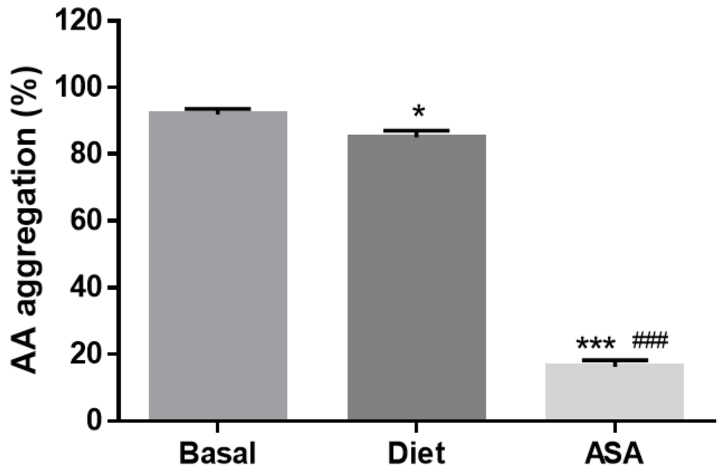

Figure 1. Effect of a potato peel diet (2 g/kg/d) or acetylsalicylic acid (ASA, 100 mg/d, as reference) on platelet aggregation percentages in response to arachidonic acid (AA, 150 µg/mL) stimulation, compared to baseline values in healthy volunteers after seven days of treatment. (Mean ± s.e.m., RM one-way ANOVA with Tukey's multiple comparison test. *p<0.05, ***p<0.001 vs. baseline; ###p<0.001 vs. the diet.).

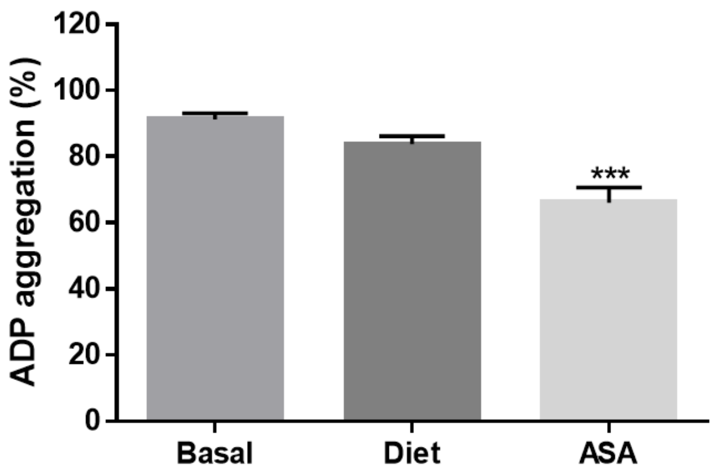

Figure 2. Platelet Aggregation in Response to Potato Peel Diet (2 g/kg/d) and Acetylsalicylic Acid (ASA, 100 mg/d) Stimulated by Adenosine Diphosphate (ADP, 10 µM) in Healthy Volunteers After Seven Days of Treatment. (Mean ± s.e.m., Friedman test with Tukey's multiple comparison. ***p<0.001 vs. baseline.).

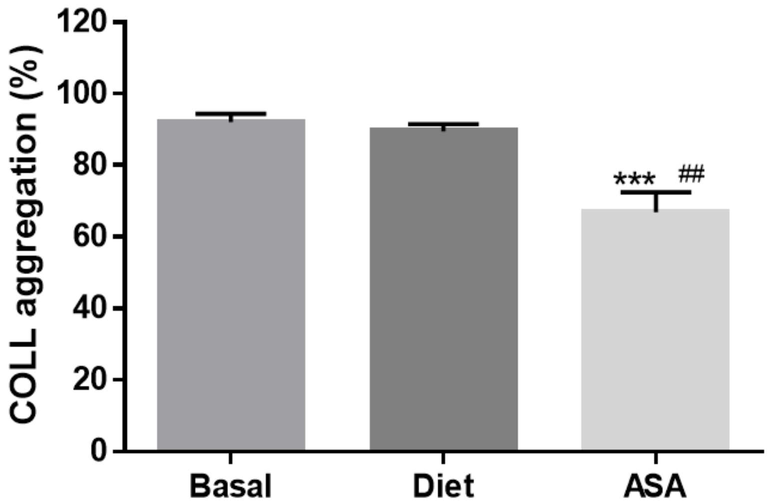

Figure 3. Platelet Aggregation in Response to Potato Peel Diet (2 g/kg/d) and Acetylsalicylic Acid (ASA, 100 mg/d) Stimulated by Collagen (COLL, 10 μg/mL) in Healthy Volunteers After Seven Days of Treatment. (Mean ± s.e.m., Friedman test with Tukey's multiple comparison. ***p<0.05 vs. baseline, ##p<0.005 vs. the diet.)

This study utilized various agonists to induce platelet aggregation and assessed changes in aggregation percentages after introducing a potato peel-rich diet. The intervention significantly reduced platelet aggregation when stimulated by arachidonic acid (AA). Although reductions in aggregation were noted with ADP and COL stimulation, statistical significance was not achieved. As expected, ASA exhibited its inhibitory effect on aggregation with the most pronounced impact observed against AA.

Discussion

In this study, the effects of a diet rich in potato peel over a seven-day period on platelet aggregation in healthy volunteers were investigated. Results indicated that a potato peel-enriched diet resulted in a slight but statistically significant decrease in platelet aggregation when arachidonic acid (AA) was used as the stimulant. A similar trend was observed with adenosine diphosphate (ADP) and collagen (COL) stimulants, although statistical significance was not reached. As anticipated, a more pronounced antiplatelet effect was observed with ASA. This outcome suggests that a potato peel-enriched diet has the potential to preserve platelet function, providing a proactive approach to counteracting platelet adhesion to vascular intima under conditions of endothelial dysfunction, ultimately reducing the risk of atherothrombotic disorders.
The study employed a self-controlled crossover design, which is a suitable approach for examining interventions within the same participant group. This design minimizes individual variability and enables a robust comparison within subjects. Such a design is particularly advantageous for studying short-term interventions, such as dietary modifications or drug treatments.

In this study, a sample size of 12 volunteers was employed, resulting in two groups of 24 data points for each intervention. The self-controlled crossover design capitalizes on each participant serving as their own control, thereby enhancing the statistical power of the study to compensate for the relatively small sample size. Nevertheless, it is important to acknowledge the inherent limitations associated with a small sample size when interpreting the results.

To ensure intervention independence, the study monitored platelet life span and implemented a washout period. This approach is crucial in preventing carryover effects and maintaining intervention integrity.

The primary outcome measure focused on the percentage of platelet aggregation before and after treatment. The selected statistical analyses were considered appropriate for this study design, allowing the assessment of differences between interventions and means across groups. However, it is important to acknowledge the study's limitations, which include the study design, sample size, and underlying assumptions made during analysis.

Effective prevention of cardiovascular diseases relies on maintaining a balanced diet, engaging in regular exercise, and fostering positive habits. Activated platelets play a critical role in early-stage plaque formation, emphasizing the importance of dietary strategies that can influence platelet function in the prevention of atherothrombotic vascular diseases. This dietary approach offers the advantage of a lower risk of adverse effects compared to potential antiplatelet agents often used in primary prevention (20).

The influence of the potato diet on platelet aggregation, particularly its selective effect against arachidonic acid, may be linked to its potential to inhibit the synthesis of thromboxane A2. Thromboxane A2 is a powerful platelet aggregator and vasoconstrictor. This aligns with one of aspirin's antiplatelet mechanisms, where aspirin also inhibits thromboxane A2 synthesis.

While a potato diet may is less potent than aspirin (16, 21), it offers the potential advantage of a lower risk of adverse effects. Aspirin's well-documented efficacy and extensively studied mechanisms and dosages emphasize the necessity for additional research to establish the mechanisms, safety, and effectiveness of the potato diet's potential antiplatelet effects, especially when compared to established medications like aspirin.

While this study has its limitations, including a small sample size consisting solely of healthy volunteers, these constraints limit the generalizability of the findings to broader populations. Nonetheless, the results underscore the promising potential of potato peels as a nutritional strategy to maintain platelet function in healthy individuals. As this work represents a preliminary study assessing the effects of a potato peel diet and ASA on platelet aggregation, it's important to exercise caution when interpreting the results due to the small sample size and the open-label nature of the study.

While studies exploring metabolites and diets with antiplatelet properties may vary due to differences in study populations and small sample sizes, they consistently highlight the preventive potential of the Mediterranean diet (2). This study, which focuses on potato peels, suggests an opportunity to broaden the spectrum of nutrients that could contribute to protection against atherothrombotic disorders.

Given that *Solanum tuberosum*, commonly known as the potato, is native to Andean countries and already constitutes a staple in their traditional diets, the potential preventive properties against atherothrombotic disorders could encourage greater consumption of potato peels worldwide. Additionally, if *S. tuberosum* indeed displays antihypertensive properties in human studies, it could stimulate the economic growth of the production chain centered around this valuable resource (10, 21).

Previous research has highlighted the role of polyphenolic compounds, such as caffeic acid and chlorogenic acid, in driving the observed antiplatelet properties of *S. tuberosum* (5). Their antioxidant capabilities might account for the observed antiaggregant effects, although additional mechanisms are likely at play. For instance, mechanisms linked to platelet cyclase/cAMP/PKA activation pathways, which regulate platelet function, might contribute (22-23). Additionally, compounds like the serine protease 'StSBTc-3,' which exhibits fibrinogenolytic activity (24), may also play a role.

The potato diet's selective effect against arachidonic acid (AA) suggests that its active components might inhibit the synthesis of platelet prostanoid thromboxane A2 (5). While its potency may be lower than that of acetylsalicylic acid (ASA), the lower probability of adverse effects makes it an intriguing avenue that warrants further investigation. Furthermore, varying polyphenol contents among different varieties of *S. tuberosum* have been documented (25). This study aligns with Buitrago et al.'s findings, which suggested that the 'pastusa' variety, rich in caffeic acid, exhibited greater antiaggregant activity against AA (5). Nevertheless, additional research is necessary to fully understand the relationship between different *S. tuberosum* varieties and their impact on platelet function.

Variations in glycoalkaloid content among *S. tuberosum* varieties have also been recognized (13), which is a crucial factor in establishing the safety of human consumption. Previous studies involving this variety have confirmed that glycoalkaloid content falls within acceptable limits, further supporting the case for potato peel consumption (8, 9).

The European Food Safety Authority (EFSA) has emphasized the significance of a balanced diet for cardiovascular health, citing compelling evidence for the antiplatelet effects of long-chain polyunsaturated fatty acids—particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—as well as plant polyphenols (2, 10). In alignment with these findings, S. tuberosum emerges as a potential representative of this latter group.

Conclusions

The administration of a diet rich in potato peel to healthy individuals has shown potential in reducing platelet aggregation, preserving platelet function in tissues vulnerable to endothelial dysfunction. These actions may be pivotal in preventing atherothrombotic disorders, with broader implications for cardiovascular health and dietary interventions, highlighting the promise of potato peel consumption in supporting heart health.

This study offers insights into the impact of dietary choices on platelet function, especially in the context of cardiovascular health. Consuming a diet rich in potato peel led to a significant reduction in platelet aggregation among healthy participants. This outcome holds promise as a proactive strategy to safeguard platelet function, particularly in environments characterized by endothelial dysfunction, a precursor to platelet adhesion and aggregation. By modulating platelet reactivity, such dietary interventions have the potential to contribute to the prevention of atherothrombotic disorders, which are marked by thrombus formation and cardiovascular events.

While these initial findings are encouraging, there's a need for further exploration to fully understand the precise mechanisms underlying the influence of potato peel components on platelet function. Gaining a comprehensive understanding of the interactions between polyphenolic compounds and other bioactive constituents in potato peel, as well as their impact on platelet activation pathways, could provide valuable insights. Moreover, investigating potential synergistic effects between potato peel consumption and other dietary factors known to impact cardiovascular health, such as the Mediterranean diet, may reveal holistic dietary recommendations for a more comprehensive approach to addressing the risk of atherothrombotic disorders.

The observed variations in antiaggregant activity among diverse S. tuberosum varieties underscore the intricate nature of dietary interventions and emphasize the significance of accounting for genetic diversity within food sources. Subsequent studies should delve into the mechanistic differences among these varieties to provide guidance for personalized dietary recommendations.

From a broader perspective, advocating for increased consumption of potato peels aligns with the principles of sustainable and locally sourced nutrition, particularly in regions where *S. tuberosum* is a dietary staple. In addition to its cardiovascular benefits, this potential dietary approach resonates with the ethos of promoting traditional foods that enrich both health and culture.

In summary, this study provides insights into the potential cardiovascular benefits of incorporating potato peel into the diet. The findings suggest the need for ongoing research to fully understand the therapeutic potential of this natural dietary component. By advancing our understanding of the intricate interplay between diet and platelet function, significant steps are taken toward a more comprehensive approach to preventing atherothrombotic disorders and promoting holistic cardiovascular health.

Conflict of interest: None of the authors have conflicts of interest related to this study.

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