Platelet Aggregation Inhibition: An Evidence-Based Systematic Review on the Role of Herbs for Primary Prevention Based on Randomized Controlled Trials

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Abstract

Background: Platelet aggregation is a crucial mechanism in the progression of atherothrombotic events. This systematic review aims to introduce the plants studied in healthy people as the primary prevention to inhibit platelet aggregation. We also discuss possible mechanisms that are involved in the inhibition of platelet aggregation.

Methods: A systematic search on the electronic medical databases from 1970 to February 2020 was performed. The selected keywords were: “herb”, “plant”, “platelet aggregation”, “platelet activation”, “clinical trial”, “randomized” and “controlled”.

Results: The result of the initial search was a pool of 136 articles. After initial abstract reviewing, there were 55 relevant articles. Finally, 28 eligible records fulfilled our inclusion criteria to enter the qualitative synthesis process.

Conclusion: Out of the 10 plants evaluated in the clinical trials, nine plants had inhibitory effects on platelet aggregation. Most of the reviewed plants, including tomato (Solanum lycopersicum L), garlic (Allium sativum), kiwifruit (Actinidia deliciosa), cacao (Theobroma cacao), grape (Vitis vinifera), ginkgo (Ginkgo biloba), flaxseed (Linum usitatissimum), sea buckthorn berry (Hippophae), and argan (Argania spinose) could be potential sources for the primary prevention of atherothrombotic events at an appropriate dosage. Finally, we do not consider phytoceuticals as a replacement for the guideline-directed medical treatment.

Keywords
● Systematic review ● Herbal medicine ● Plants ● Platelet aggregation ● Primary prevention

Introduction

Atherothrombotic events, such as strokes and coronary heart disease (CHD), cause high mortality and morbidity rates in the human population.1 Platelet aggregation plays a substantial role in their pathogenesis.2 The pathogenesis of atherothrombotic events encompasses the interactive processes of atherosclerotic

What’s Known

• Platelet aggregation plays an important role in atherothrombotic events, such as cerebrovascular and cardiovascular events.
• Potential adverse effects of established antiplatelet therapies encourage us to evaluate the possible role of medicinal herbs in the primary prevention of cardiovascular disease in the general population.

What’s New

• Of the 10 plants evaluated in clinical trials, nine plants had inhibitory effects on platelet aggregation, including tomato, garlic, kiwifruit, cacao, grape, ginkgo, flaxseed, sea buckthorn berry, and argan.
• Phytoceuticals could have a potential effect on the primary prevention of atherothrombotic events at an appropriate dosage, but not as a replacement for the current treatment.
lesions and the development of thrombi following platelet activation at the injured vascular site. The concomitant increase in platelet activity is associated with a higher risk of atherothrombotic events. Therefore, inhibiting platelet aggregation is the cornerstone of protection against CHD and strokes, and it would decrease the risk of atherothrombotic events. Antiplatelet drugs, such as aspirin, clopidogrel, and ticlopidine, are a part of the current clinical practice to treat and prevent CHD and strokes.

Plants have been the primary source of the discovery and development of the active ingredients of medicines. Plant-based treatments have resulted in numerous clinical trials. Several in vitro, in vivo, and human studies have been conducted to assess the impact of medicinal herbs on the inhibition of platelet aggregation. In vitro studies demonstrated the reduction of platelet aggregation by andrographis, feverfew, garlic, ginger, ginkgo, ginseng, horse chestnut, and turmeric. Cranberry, strawberry, green tea, pomegranate juice, and onion, wine, and grape juice. Clinical trials reported antiplatelet effects for garlic, ginger, ginkgo, and tomato.

The potential adverse effects of standard antiplatelet therapies encourage us to use medicinal herbs, particularly for the primary prevention of cardiovascular disease. Various mechanisms have been proposed for inhibiting platelet aggregation by medicinal herbs, including the inhibition of the collagen and adenosine diphosphate (ADP) pathway, an increase in the basal levels of tyrosine phosphorylation, the inhibition of cyclooxygenase activity, the inhibition of thromboxane A2 production, and the reduction of intracellular Ca2+ mobilization. The current medical literature still lacks a systematic review on the antiplatelet activity of herbs. We conducted this systematic review to report the plants that can inhibit platelet aggregation. In other words, this review can answer whether plants can be used as the primary prevention of atherothrombotic events or not.

### Materials and Methods

#### Identification of Studies

An electronic literature systematic search was conducted in PubMed (Medline, PubMed central), Scopus, Cochrane, Web of Science Core Collection, and Embase from the year 1970 to November 2020. We developed separate search strategies for each database, which can be seen in table 1 as an example for PubMed. The reference lists of eligible articles were manually searched to find additional relevant studies. The search terms in this study included "plant", "herb", "platelet aggregation", and "platelet activation". There was no restriction on language or date of publication.

#### Eligibility Criteria

The PICOS eligibility criteria were:

- **Population**: healthy volunteers or participants with atherosclerosis risk factors
- **Intervention**: any herbs
- ** Comparator**: placebo or herb
- **Outcomes**: inhibition of platelet aggregation
- **Study design**: randomized controlled trials

#### Inclusion and Exclusion Criteria

We included the studies that met the following criteria: 1) randomized controlled trials on healthy volunteers comparing any herb with placebo, another herb, or the same herb with a different dosage, 2) evaluating any herb that can inhibit platelet aggregation, 3) administration of herbal medicines orally, and 4) publications with available abstracts and full-texts. We excluded in vitro or in vivo studies, review studies, systematic reviews, studies without controls, clinical trials on preparations containing more than one herbal remedy, commentaries, letters to editors, protocols, abstracts, and non-English full-text studies.

### Table 1: The strategy used for searching in PubMed

| Database (Medline, PubMed central) | Search strategy | Number of Articles |
|------------------------------------|-----------------|-------------------|
| Text word ("Plants"[Mesh]) AND the title/abstract ("Platelet Activation"[Mesh]) | 990 |
| Text word ("Plants"[Mesh]) AND the title/abstract ("Platelet Activation"[Mesh]) Filters: Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase III; Clinical Trial, Phase IV; Clinical Trial, Veterinary, Randomized Controlled Trial | 96 |
| Text word ("Plants"[Mesh]) AND the title/abstract ("Platelet Activation"[Mesh]) Filters: Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase III; Clinical Trial, Phase IV; Clinical Trial, Veterinary, Search ("Plants"[Mesh]) AND "Platelet Activation"[Mesh] Filters: Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase III; Clinical Trial, Phase IV; Clinical Trial, Veterinary; English | 89 |
| Full-text articles assessed for eligibility | 46 |
| Related | 28 |
Study Selection

After removing the duplicates, two authors (SN, NO) separately evaluated the titles/abstracts to include the relevant articles in the study. The same authors read the full texts of the selected articles to assess the eligibility criteria. In case of any doubt or disagreement, the authors would discuss the respective study. The management of the search results was carried out by EndNote software (EndNote X8; Clarivate Analytics, Philadelphia, PA, United States of America).

Data Extraction and Quality Assessment of the Studies

The authors had a predefined checklist, and two authors (SN and NO) independently extracted the data. Data extraction was done using Microsoft Excel (Microsoft, USA). The data extracted from each study included: the study publication year, the number of participants, studied plant, comparators, part of the plant used in the study, drug dosage/form, duration of treatment, and outcome. We used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist for the qualitative evaluation of the studies.24

Synthesis of Results

The results of the studies and their characteristics were summarized and compared in tables 2 and 3.

This study was reported under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.25 Due to the heterogeneity of the studies included in this review, we did not perform the meta-analysis.

Results

The flowchart of the systematic search is demonstrated in figure 1. Out of 136 records, 28 articles were entered into the qualitative synthesis for critical appraisal and data extraction. All the studies had case and control groups. The characteristics and the main results of all the studies are outlined in table 2. Following data extraction, ten plants, including tomato, garlic, kiwifruit, cacao, grape, strawberry, ginkgo, flaxseed, sea buckthorn berry, and argan, were reviewed in 28 studies. Except for strawberry, the other plants had inhibitory effects on platelet aggregation to some extent. A number of these plants, including garlic, cocoa, grape, ginkgo, and flaxseed, had shown a diverse effect on inhibiting platelet aggregation.

These plants were categorized into three main groups according to bioactive compounds contributing to the antiplatelet effect. These categories were “polyphenols”, “organosulfur”, and “unsaturated fatty acids” (table 3).
Table 2: Eligible randomized clinical trials focused on the effect of an herb on platelet aggregation inhibition

| Study                  | Plant comparator         | Number of participants | Comparator                          | Part of plant                      | Drug Dosage/form                                      | Duration of treatment | Results                                                                                                                                 |
|------------------------|--------------------------|------------------------|-------------------------------------|------------------------------------|--------------------------------------------------------|-----------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| Palomo I<sup>16</sup>  | Tomato                   | 99                     | Placebo                            | Tomato Pomace Extract             | Different doses of tomato pomace extract (1 g, 2.5 g/ onceday) | 5 days                | Consumption of aqueous extract of tomato pomace exerted an inhibitory activity on platelet aggregation.                                |
| Lazarus SA<sup>26</sup> | Tomato juice, 250 mL/day | 20                     | Placebo                            | Tomato juice, 250 mL/day           | Tomato juice, 250 mL/day                               | 3 weeks               | Platelet aggregation decreased following supplementation with tomato juice as compared with the placebo group.                      |
| O’Kennedy N<sup>27</sup> | Tomato extract           | 90                     | Placebo                            | Tomato extract syrup, 200 mL, single dose | Tomato extract syrup, 200 mL, single dose               | 3 hours               | Significant reductions in ex vivo platelet aggregation induced by ADP and collagen were observed three hours after supplementation.   |
| Morris J<sup>28</sup>   | Garlic                   | 14                     | Placebo                            | Oil extract (equivalent to 15 g of raw garlic) | 1 gelatin capsule/day                                  | 5 days                | There were no significant differences in platelet aggregation with adenosine diphosphate, platelet-activating factor (PAF), or collagen between groups. |
| Steiner M<sup>29</sup>  | Aged garlic extract      | 15                     | Placebo                            | Capsule 800 mg of Aged garlic extract | Capsule 800 mg of Aged garlic extract 3×TDS            | 11 months             | AGE administration produced inhibition of some of the platelet functions.                                                            |
| Steiner M<sup>30</sup>  | Aged garlic extract      | 34                     | Placebo                            | 3, 6, 9 capsules/day (each 800 mg Aged garlic extract) | 3, 6, 9 capsules/day (each 800 mg Aged garlic extract) | 6 weeks×3 duration   | AGE exerted selective inhibition on platelet aggregation and adhesion.                                                              |
| Kiesewetter H<sup>31</sup> | Powdered garlic         | 60                     | Placebo                            | Coated tablets (400 mg of powdered garlic) /QID | Coated tablets (400 mg of powdered garlic) /QID | 4 weeks               | The parallel-group comparison (garlic versus placebo) revealed a significantly different ratio of circulating platelet aggregates after four weeks of treatment. |
| Scherbart G<sup>32</sup> | Raw garlic               | 18                     | Placebo                            | Raw garlic                         | Raw garlic                                           | 1 week                | Platelet function was not impaired by single and repeated oral consumption of raw garlic.                                        |
| Legnani C<sup>33</sup>  | Dried garlic powder     | 12                     | Placebo                            | Tablet 900 mg/day                  | Tablet 900 mg/day                                    | 14 days               | Platelet aggregation values were significantly lower after 7 and 14 days of garlic treatment.                                         |
| Karlsen A<sup>34</sup>  | Antioxidant-rich diet group, habitual diet group  | 102                    | Antioxidant-rich diet group, habitual diet group | Fruit | Antioxidant-rich diet group, habitual diet group | 8 weeks               | In the kiwifruit group, a 15% reduction in platelet aggregation was observed.                                                        |
| Brevik A<sup>35</sup>   | Kiwifruit doses in a different order  | 24                     | Kiwifruit doses in a different order  | Fruit | One kiwifruit per day in the first period, two in the second, or two per day in the first period, one in the second | 4 weeks×2             | Green and golden kiwifruit extracts inhibit both ADP and collagen-induced whole blood platelet aggregation (to different degrees). |
| Duttaroy AK<sup>36</sup> | Kiwifruit extract       | 30                     | Kiwifruit doses in a different order  | Kiwifruit extract | Period 1: group A: 2 kiwi /d, group B: 3 kiwi /d, group C: 3 kiwi /d, group D: 2 kiwi /d | 28 days periods separated by at least two-week washout periods | Kiwifruit produced effective inhibiting effects on platelet aggregation induced by collagen and ADP in human volunteers. |
| Innes AJ<sup>37</sup>   | Theobroma cacao L.       | 30                     | White chocolate (no cacao) Milk chocolate (20% cacao) Dark Chocolate (75% cacao content) | 100 g/day of dark chocolate, single-dose | 100 g/day of dark chocolate, single-dose | 4 hours               | Dark chocolate inhibited collagen-induced platelet aggregation in platelet-rich plasma. |

*Note: ADP = adenosine diphosphate, PAF = platelet-activating factor.*
| Study          | Plant comparator | Comparator | Number of participants | Comparator Part of plant | Number of participants | Drug Dosage/form | Part of plant | Duration of treatment | Results                                                                 |
|---------------|------------------|------------|------------------------|--------------------------|------------------------|------------------|---------------|----------------------|-------------------------------------------------------------------------|
| Ottaviani JI  | 35               | Placebo (CF-free control capsules) | 34                      | Cacao extract of seed     | 60 mg daily            | 2-4 capsules     | 12 weeks       | There were no significant differences in platelet function between groups. |
| Pozniak D     | 30               | White chocolate Dark chocolate  | 30                      | Cacao extract of seed     | 240 mL single-dose     | 12 weeks       | Six hours      | Platelet aggregation-induced ADP was significantly reduced two hours after cacao consumption but increased after caffeine and water consumption. |
| Rein D        | 37               | Caffeine-containing control beverage or water | 30                      | Cacao beverage            | 60 g, single-dose     | Six hours      | Platelet micro-particle formation decreased two and six hour after cacao consumption but increased after caffeine and water consumption. |
| Kevill JG     | 38               | Vitis vinifera (Grape) | 10                      | Juice of the grape seed   | 120 g, single-dose     | Six hours      | Platelet aggregation-induced ADP was significantly reduced two hours after cacao consumption but increased after caffeine and water consumption. |
| Bazan-Salinas Il  | 39              | Arachis hypogaea oils in one group and no oil in other | 30                      | Juice of the grape seed   | 5-7.5 mg/Kg/day       | One week       | Platelet aggregation-induced ADP was significantly decreased ADP-stimulated platelet reactivity at one, two, and six hours following intake. |
| Polagruto JA  | 40               | Placebo Flavanol-Rich Grapeseed Extract (FRGSE) | 23                      | Flavanol-rich extract     | 2×200 mg capsules, single-dose | Six hours      | The FRGSE supplement, but not the placebo, significantly decreased ADP-stimulated platelet reactivity at one, two, and six hours following intake. |
| Ras RT        | 41               | Placebo Grape seed extract (GSE) | 70                      | Grape seed extract       | 1 capsule /day each capsule containing 300 mg GSE | Eight weeks      | Grape seed extract intervention did not change platelet aggregation as induced by several agonists when compared with placebo. |
| Köhler S      | 42               | Ginkgo biloba | 50                      | Dry extract Ginkgo biloba | Table 120 mg/2 day     | Seven days, crossover design in three weeks of washout | Ginkgo tablet inhibits platelet aggregation by inhibiting thromboxane B2 production. |
| Djurica D     | 43               | Strawberry | 25                      | Freeze-dried strawberry powder | Powder, 50 mg daily | One week       | Platelet activation markers were not significantly different between groups. |
Out of 10 plants evaluated in the clinical trials, nine had inhibitory effects on platelet aggregation. Studies suggest that polyphenols are the major components involved in the inhibition of platelet aggregation. Based on duration, dosage, and route of administration, plants have shown various effects on the inhibition of platelet aggregation.

In vitro, high doses of herbal compounds with antiplatelet activity would suppress platelet aggregation. On the contrary, low dose concentrations in vivo would have a minor effect. The antiplatelet activity of herbal compounds could be due to the synergistic function of all properties, rather than individual components.

Several clinical trials have shown that tomato, cacao, grape, kiwi, and ginkgo have an inhibitory effect on platelet aggregation. Based on these studies, the major components involved in the inhibition of platelet aggregation in these plants are polyphenols. Polyphenols are common bioactive compounds mainly derived from fruits, vegetables, and traditional medicinal herbs. Previous studies reported that polyphenols could influence the cardiovascular system by lowering blood pressure, improving endothelial function, increasing antioxidant defenses, inhibiting low-density lipoprotein oxidation, and reducing inflammatory responses. In most of the in vitro and in vivo studies, polyphenols had inhibitory effects on platelet aggregation to some degree.

The inhibitory effect of polyphenols supplementation on platelet aggregation is attributed to several different molecular mechanisms. Tomato extract, cacao, kiwi, and ginkgo inhibit collagen- and ADP-induced platelet aggregation. Grape juice and grape seed extracts inhibit platelet aggregation induced by collagen and thrombin-receptor agonist peptide (TRAP) and increase basal levels of tyrosine phosphorylation.

In vitro experiments have demonstrated that the inhibition of platelet aggregation by phenolic compounds is generally dose-dependent. Furthermore, the effect of polyphenols on platelet aggregation in humans and animal models is strongly dependent on their absorption and metabolism. The inhibitory effect of ginkgo supplementation on platelet aggregation developed after three months. However, it had no effect within seven days of administration. Grape juice and grape seed oil have an inhibitory effect on platelet aggregation in an adequate dosage and a proper duration of treatment.
An *in vitro* study showed that extracts of grape seed and skin lead to a dose-dependent inhibition of platelet aggregation.\(^{61}\) Strawberry, as a source of polyphenols, had no inhibitory effects on platelet aggregation with a dose equal to 50 g of dried powder/day for one week.\(^{50}\) Nonetheless, this effect was observed in *in vivo* studies.\(^{10, 13}\) The estimated sufficient dose of strawberry extract to inhibit platelet aggregation in humans is about 70 mg/Kg based on an *in vivo* study,\(^{13}\) which is much higher than the prescribed dose in the randomized clinical trial (RCT) on strawberry mentioned above.\(^{43}\)

Both single\(^{27}\) and multiple doses\(^{18, 26}\) of tomato extract had a similar inhibitory effect on platelet aggregation. Interestingly, studies on a single dose of cacao\(^{34, 36, 37}\) reported significant antiplatelet effects, whereas long-term cacao administration\(^{35}\) had no inhibitory effect on platelet aggregation. One could argue that if the long-term dosage of cacao was equal to or greater than a single dosage, it might result in higher circulating concentrations of phenolic compounds, and would be effective in platelet aggregation inhibition. Moreover, the accumulation of phenolic compounds and their metabolites might occur in many tissues.\(^{62}\)

Numerous clinical trials have demonstrated that garlic would inhibit platelet aggregation. This biological property of garlic is mainly attributed to the high content of organosulfur compounds found in garlic and onion.\(^{53}\) Moreover, organosulfur compounds of garlic possess anti-atherosclerotic properties by reducing serum cholesterol levels in humans, inhibiting cholesterol biosynthesis, suppressing low-density lipoprotein (LDL) oxidation, lowering plasma fibrinogen, and increasing fibrinolytic activity.\(^{54}\)

Organosulfur compounds inhibit platelet aggregation by interfering with cyclooxygenase activity and blocking thromboxane A2 formation. This leads to suppressed intraplatelet Ca\(^{2+}\) mobilization and raised levels of intraplatelet cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).\(^{22}\)

Administration of garlic oil extract with a dose equal to 15 g of raw garlic per day for five days\(^{28}\) and raw garlic at 4.2 g/day for a week\(^{30}\) had no inhibitory effect on platelet aggregation. However, powdered garlic or aged garlic extract at 900 mg/day for two weeks,\(^{31}\) (3,6,9 capsule) \(\times800\) mg/day for six weeks for three periods of time,\(^{16}\) 400 mg/every six hours for four weeks,\(^{29}\) and (three capsule) \(\times800\) mg/every eight hours for 11 months\(^{34}\) showed inhibitory effects on platelet aggregation. According to previous studies,\(^{16, 31}\) dry extracts of garlic demonstrated more activity on platelet aggregation than the oil, which could be attributed to the higher concentrations of organosulfur compounds in the garlic powder tablets.\(^{44}\)

Several clinical trials have shown that flaxseed, argan, sea buckthorn berry, and grape seed have antiplatelet properties. Unsaturated fatty acids, including polysaturated fatty acids (PUFAs)\(^{39, 45-47, 52, 53}\) and monounsaturated fatty acids (MUFA)s,\(^{53}\) are the major components for inhibiting platelet aggregation in these plants. omega-6 (linoleic acid) and omega-3 (\(\alpha\)-linolenic acid) are two types of polysaturated fatty acids. These essential fatty acids are found in fatty seeds, nuts, and some vegetables.\(^{65}\) In this review, flaxseed oil (as a source of omega-3), sea buckthorn berry oil (as a source of omega-6 and omega-3), and argan oil containing balanced proportions of MUFA(s) (oleic acid) and PUFAs (omega-6)\(^{53}\) showed inhibitory effects on platelet aggregation. Previous studies have revealed that PUFAs can significantly prevent cardiovascular diseases.\(^{66}\)

According to animal and human studies, flaxseed, argan, and sea buckthorn decreased thrombin- and collagen-induced platelet aggregation.\(^{52, 53, 67}\)

Oil extract of flaxseed at a dose of 2 g/day for 12 weeks\(^{45}\) did not inhibit platelet aggregation.
compared with 40 g/day for 23 days. The difference in the inhibitory effects could be attributed to the fact that omega-3 fatty acids in large doses reduce platelet aggregation, but smaller amounts have modest platelet inhibitory effects.

It should be noted that garlic and ginkgo may increase the pharmacological effects of aspirin and anticoagulant agents. Thus, the patients should be warned against the concurrent use of garlic/ginkgo and anticoagulant drugs, which may increase the risk of bleeding.

The main limitation of our review is that the RCTs only studied healthy volunteers. RCTs with preparations containing more than one herbal medicine and a clinical trial with a conventional drug, as a comparator, were not included in this review. On the other hand, the sample size was not included as an eligibility criterion.

**Conclusion**

Most of the plants in this systematic review potentially have an inhibitory effect on platelet aggregation. Accordingly, these plants could be introduced as potential sources for the primary prevention of atherothrombotic events at an appropriate dosage. Achieving convincing results requires conducting further clinical trials to evaluate the efficacy and safety of herbal medicines for the prevention of cardiovascular disease.

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**Authors’ Contribution**

S.N, A.V.F, H.R, P.G, S.M.G, and N.O: Contributed to conception and design of the study. All of the authors had contribution in all phases of this study; S.N and N.O wrote the first draft; A.V.F, H.R, P.G, and S.M.G: Revised this manuscript critically for important intellectual content. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Conflict of Interest:** None declared.

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