

# 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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## 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.
- Phytochemicals 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.

## 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 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 phytochemicals as a replacement for the guideline-directed medical treatment. Large randomized double-blind clinical trials are required to evaluate the anti-platelet characteristics of these plants for the adjuvant primary prevention of cardiovascular disease.

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**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.<sup>1</sup> Platelet aggregation plays a substantial role in their pathogenesis.<sup>2</sup> The pathogenesis of atherothrombotic events encompasses the interactive processes of atherosclerotic

lesions and the development of thrombi following platelet activation at the injured vascular site.<sup>3</sup> The concomitant increase in platelet activity is associated with a higher risk of atherothrombotic events.<sup>4</sup> 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.<sup>5</sup>

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.<sup>6</sup> 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,<sup>7</sup> hawthorns,<sup>8</sup> cranberry,<sup>9</sup> strawberry,<sup>10</sup> green tea,<sup>11</sup> pomegranate juice.<sup>12</sup> *In vivo* studies found platelet aggregation inhibiting effects in herbs such as strawberry,<sup>13</sup> green tea,<sup>11</sup> onion,<sup>14</sup> wine, and grape juice.<sup>15</sup> Clinical trials reported antiplatelet effects for garlic,<sup>16</sup> ginkgo,<sup>17</sup> and tomato.<sup>18</sup>

The potential adverse effects of standard antiplatelet therapies<sup>19</sup> 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,<sup>20</sup> an increase in the basal levels of tyrosine phosphorylation,<sup>21</sup> the inhibition of cyclooxygenase activity,<sup>22</sup> the inhibition of thromboxane A2 production,<sup>17</sup> and the reduction of intracellular Ca<sup>2+</sup> mobilization.<sup>23</sup> 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	Search strategy	Number of Articles
PubMed	Text word (“Plants”[Mesh]) AND the title/abstract (“Platelet Activation”[Mesh])	990
(Medline, PubMed central)	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.<sup>24</sup>

### Synthesis of Results

The results of the studies and their characteristics were summarized and compared

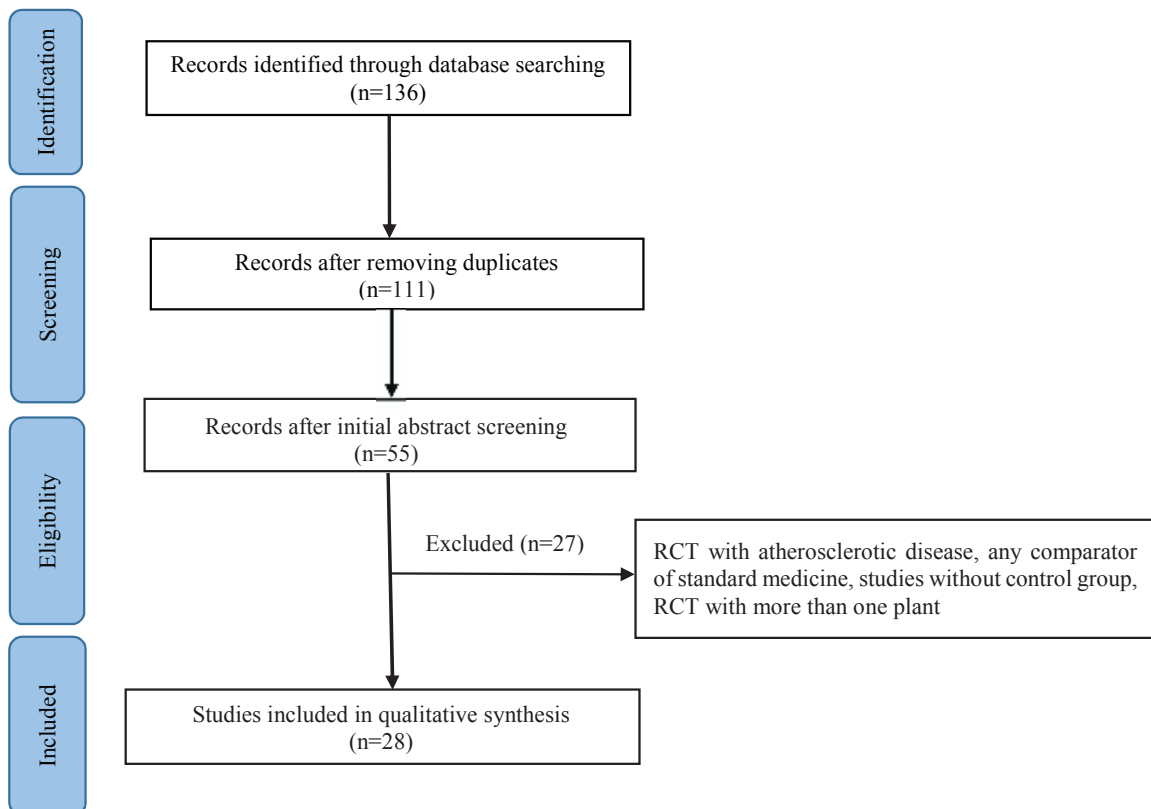
in tables 2 and 3.

This study was reported under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>25</sup> 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).



**Figure 1:** A Diagram of the systematic search according to PRISMA shows the exclusion and inclusion of the studies.

**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>18</sup>	Tomato	99	Placebo	Tomato Pomace Extract	Different doses of tomato pomace extract (1 g, 2.5 g/once daily)	5 days	Consumption of aqueous extract of tomato pomace exerted an inhibitory activity on platelet aggregation.
Lazarus SA <sup>26</sup>		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>		90	Placebo	Tomato extract	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	1 gelatin capsule/day (equivalent to 15 g of raw garlic)	5 days	There were no significant differences in platelet aggregation with adenosine diphosphate, platelet-activating factor (PAF), or collagen between groups.
Steiner M <sup>23</sup>		15	Placebo	Aged garlic extract	Capsule 800 mg of Aged garlic extract 3xTDS	11 months	AGE administration produced inhibition of some of the platelet functions.
Steiner M <sup>16</sup>		34	Placebo	Aged garlic extract	3, 6, 9 capsule/day (each 800 mg Aged garlic extract)	6 weeksx3 duration	AGE exerted selective inhibition on platelet aggregation and adhesion.
Kiesewetter H <sup>29</sup>		60	Placebo	Powdered garlic	Coated tablets (400mg 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.
Scharbert G <sup>30</sup>		18	Placebo	Raw garlic	Raw garlic, 4.2 g/day	1 week	Platelet function was not impaired by single and repeated oral consumption of raw garlic
Legnani C <sup>31</sup>		12	Placebo	Dried garlic powder	Tablet 900 mg/day	14 days	Platelet aggregation values were significantly lower after 7 and 14 days of garlic treatment.
Karlsen A <sup>32</sup>	Kiwifruit	102	Antioxidant-rich diet group, habitual diet group	Fruit	3 kiwifruits per day (195 g fruit)	8 weeks	In the kiwifruit group, a 15% reduction in platelet aggregation was observed.
Brevik A <sup>33</sup>		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 weeksx2	Green and golden kiwifruit extracts inhibit both ADP and collagen-induced whole blood platelet aggregation (to different degrees).
Duttaroy AK <sup>20</sup>		30	Kiwifruit doses in a different order	Kiwifruit extract	Period 1: group A: 2 kiwi /d, group B: 3 kiwi/d Period 2: group A: 3/d, group B: 2/day	28 days periods separated by at least two-week washout periods	Kiwi fruit produced effective inhibiting effects on platelet aggregation induced by collagen and ADP in human volunteers.
Innes AJ <sup>34</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	4 hours	Dark chocolate inhibited collagen-induced platelet aggregation in platelet-rich plasma.

Study	Plant comparator	Number of participants	Comparator	Part of plant	Drug Dosage/form	Duration of treatment	Results
Ottaviani JI <sup>35</sup>		34	Placebo (CF-free control capsules)	Cacao extract of seed	Ranging from 2-4 capsules (corresponding to 1000 to 2000 mg/d cacao flavanols) during weeks 1-3	12 weeks	There were no significant differences in platelet function between groups.
Ostertag LM <sup>36</sup>		42	White chocolate	Dark chocolate	60 g, single-dose	Six hours	Platelet aggregation-induced ADP was significantly reduced two hours after consumption of dark chocolate.
Rein D <sup>37</sup>		30	Caffeine-containing control beverage or water	Cacao beverage	240 mL, single-dose	Six hours	Platelet micro-particle formation decreased two and six hours after cacao consumption but increased after caffeine and water consumption.
Keevil JG <sup>38</sup>	<i>Vitis vinifera</i> (Grape)	10	Orange and grapefruit juices	Juice of purple grape	Grape Juice, 5-7.5 mg/Kg/day	One week	Purple grape juice reduced the whole blood platelet aggregation induced by collagen.
Bazan-Salinas IL <sup>39</sup>		30	Arachis hypogaea oils in one group and no oil in other	Oil of the grape seed	1 g/d, Oil of grape seed	Seven days	Consumption of plant oils from grape seeds and peanuts had a lowering effect on platelet aggregation.
Polagruto JA <sup>40</sup>		23	Placebo	Flavanol-Rich Grapeseed Extract (FRGSE)	2x200 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 <sup>41</sup>		70	Placebo	Grape seed extract (GSE)	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 <sup>42</sup>	<i>Ginkgo biloba</i>	50	Placebo	Dry extract from Ginkgo biloba leaves	Tablet 120 mgx2 /day	Seven days, of crossover treatment, with three weeks of washout	None showed any evidence of an inhibition of blood coagulation, or platelet aggregation.
Kudolo GB <sup>17</sup>		12	Placebo	Root	Tablet, 20mg /day	Three months	Ginkgo tablet inhibits platelet aggregation by inhibiting thromboxane B2 production.
Djurica D <sup>43</sup>	Strawberry	25	Placebo	Freeze-dried strawberry powder	Powder, 50 g daily	One week	Platelet activation markers were not significantly different between groups.



Study	Plant comparator	Number of participants	Comparator	Part of plant	Drug Dosage/form	Duration of treatment	Results
Allman MA <sup>44</sup>	<i>Linum usitatissimum</i> (Flaxseed)	11	Sunflower seed oil	Flaxseed oil	40 g /d flaxseed oil	23 days	Aggregation response induced by collagen was decreased in the flaxseed oil groups.
Kaul N <sup>45</sup>	(Flaxseed)	86	Fish oil, hemp seed oil, placebo	Flaxseed oil	Capsule 1 g×2, flaxseed oil	12 weeks	Flaxseed did not alter platelet aggregation.
Edel AL <sup>46</sup>		40	Different doses of flaxseed	Milled flaxseed 10 g, 20 g, 30 g, or 40 g	10 g, 20 g, 30 g, or 40 g /d in four groups	30 days	There were no changes in platelet aggregation, even at the highest dose of flaxseed.
Johansson AK <sup>47</sup>	Sea buckthorn berry	12	Coconut oil	Extracted oil of berry	Capsule 500 mg×10/ day (5g /d)	Four weeks	A clear decrease in the rate of ADP-induced platelet aggregation was observed in the oil of the Sea buckthorn berry group.
Velmunagan S <sup>48</sup>	<i>Argania spinosa</i> (Argan)	39	Butter	Oil of kernels of Argania Spinosa	Argan oil 25 mL /day	Three weeks	In the argan oil group, thrombin-induced platelet aggregation was lower.

## Discussion

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.<sup>54</sup> The antiplatelet activity of herbal compounds could be due to the synergistic function of all properties, rather than individual components.<sup>55</sup>

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.<sup>56</sup> In most of the *in vitro* and *in vivo* studies, polyphenols had inhibitory effects on platelet aggregation to some degree.<sup>57</sup>

The inhibitory effect of polyphenols supplementation on platelet aggregation is attributed to several different molecular mechanisms. Tomato extract,<sup>58</sup> cacao,<sup>59</sup> kiwi,<sup>20</sup> and ginkgo<sup>49</sup> 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.<sup>21</sup>

*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.<sup>60</sup> The inhibitory effect of ginkgo supplementation on platelet aggregation developed after three months.<sup>17</sup> However, it had no effect within seven days of administration.<sup>42</sup> Grape juice<sup>38</sup> and grape seed oil<sup>39</sup> have an inhibitory effect on platelet aggregation in an adequate dosage and a proper duration of treatment.

**Table 3:** Bioactive contributing components to the inhibition of platelet aggregation

Component	Plant	Study
Polyphenol	Grape, grape seed	41
	Theobroma cacao L.	36
	Tomato	18
	Ginkgo biloba	49
	Kiwi	32
	Sea buckthorn berry	50
	Strawberry	10
	Garlic	51
Organosulfur	Garlic	51
Unsaturated fatty acids	Flaxseed (Omega-3)	46, 45, 52
	Argan (Omega-6, oleic acid)	53
	Sea buckthorn berry (Omega-3, Omega-6)	47
	Grapeseed	39

An *in vitro* study showed that extracts of grape seed and skin lead to a dose-dependent inhibition of platelet aggregation.<sup>61</sup> 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.<sup>50</sup> Nonetheless, this effect was observed in *in vivo* studies.<sup>10, 13</sup> The estimated sufficient dose of strawberry extract to inhibit platelet aggregation in humans is about 70 mg/Kg based on an *in vivo* study,<sup>13</sup> which is much higher than the prescribed dose in the randomized clinical trial (RCT) on strawberry mentioned above.<sup>43</sup>

Both single<sup>27</sup> and multiple doses<sup>18, 26</sup> of tomato extract had a similar inhibitory effect on platelet aggregation. Interestingly, studies on a single dose of cacao<sup>34, 36, 37</sup> reported significant antiplatelet effects, whereas long-term cacao administration<sup>35</sup> 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.<sup>62</sup>

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.<sup>63</sup> 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.<sup>64</sup>

Organosulfur compounds inhibit platelet aggregation by interfering with cyclooxygenase activity and blocking thromboxane A<sub>2</sub> formation. This leads to suppressed intraplatelet Ca<sup>2+</sup> mobilization and raised levels of intraplatelet

cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).<sup>22</sup>

Administration of garlic oil extract with a dose equal to 15 g of raw garlic per day for five days<sup>28</sup> and raw garlic at 4.2 g /day for a week<sup>30</sup> had no inhibitory effect on platelet aggregation. However, powdered garlic or aged garlic extract at 900 mg/day for two weeks,<sup>31</sup> (3,6,9 capsule) ×800 mg/day for six weeks for three periods of time,<sup>16</sup> 400 mg/every six hours for four weeks,<sup>29</sup> and (three capsule) ×800 mg/every eight hours for 11 months<sup>34</sup> showed inhibitory effects on platelet aggregation. According to previous studies,<sup>16, 31</sup> 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.<sup>44</sup>

Several clinical trials have shown that flaxseed, argan, sea buckthorn berry, and grape seed have antiplatelet properties. Unsaturated fatty acids, including polyunsaturated fatty acids (PUFAs)<sup>39, 45-47, 52, 53</sup> and monounsaturated fatty acids (MUFAs),<sup>53</sup> are the major components for inhibiting platelet aggregation in these plants. omega-6 (linoleic acid) and omega-3 (α-linolenic acid) are two types of polyunsaturated fatty acids. These essential fatty acids are found in fatty seeds, nuts, and some vegetables.<sup>65</sup> 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 MUFAs (oleic acid) and PUFAs (omega-6)<sup>53</sup> showed inhibitory effects on platelet aggregation. Previous studies have revealed that PUFAs can significantly prevent cardiovascular diseases.<sup>66</sup>

According to animal and human studies, flaxseed, argan, and sea buckthorn decreased thrombin- and collagen-induced platelet aggregation.<sup>52, 53, 67</sup>

Oil extract of flaxseed at a dose of 2 g/day for 12 weeks<sup>45</sup> did not inhibit platelet aggregation

compared with 40 g/day for 23 days.<sup>44</sup> 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.<sup>68</sup> 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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