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Review

A Review on Platelet Aggregation Inhibition Activity of Spices, Condiments and Nuts

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ABSTRACT

Platelet activation and aggregation play a crucial role in thrombosis and cardiovascular events. Anti-platelet agents are used to inhibit platelet activation and reduce the risk of these events. However, consumption of the synthetic anti-platelet agents has own adverse effects. Interestingly, spices and condiments along with nuts are rich sources of bioactive compounds that have potential anti-platelet effects. In view of this, an attempt was made to find out those spices and nuts which have shown platelet aggregation inhibition effects either in vitro or in vivo. Some of the spices having anti-platelet effect were turmeric, clove, onion, garlic, nutmeg, ginger, saffron, cumin, carom, coriander etc. Some of the nuts were chilgoza pine, walnut, baru almond, betel nut etc. These plants are rich in therapeutic compounds belonging to various secondary metabolites for example, phenolics, terpenoids, flavanoids, alkaloids, steroids etc. and may provide potential benefits for reducing platelet activation and the risk of cardiovascular events. However, further research is warranted to explore the efficacy, specific mechanisms and dosage of the compounds present in these spices and nuts through clinical studies to validate their anti-platelet activities.

KEYWORDS: *Curcuma longa,* Ginger, Chilgoza Pine, Cardamom, Walnut

INTRODUCTION

Platelets play a crucial role in haemostasis, the process of blood clot formation. However, excessive platelet activation and aggregation can lead to the formation of blood clots which could be harmful and increase the risk of cardiovascular events such as heart attack and stroke. Anti-platelet agents are used to inhibit platelet activation and aggregation, thereby reducing the risk of thrombosis[1-2]. Some of the common drugs used for this purpose are clopidogrel, aspirin, and ticlopidine which are associated with own side effects[3-4]. Therefore, need for natural anti-platelet agents seem appropriate. In this regard, plants are the best choice since time immemorial[5].

Spices, condiments and nuts have been a part of diet since ancient times. They are not only consumed for imparting flavour and aroma but also used for their nutritional as well as medicinal qualities[6]. Several nuts and spices have been shown to possess platelet aggregation inhibition activity as these are rich sources of bioactive compounds that include phenolic compounds, flavonoids, terpenes, and alkaloids. Various scientific studies have identified the mechanisms behind the inhibition of platelet activation and aggregation through spices and nuts. Some of the prominent mechanisms are inhibition of platelet adhesion and aggregation, suppression of thromboxane A2 (TXA2) production, inhibition of cyclooxygenase (COX) enzymes,

modulation of calcium signalling pathways, and interference with platelet signalling molecules etc.[7]. Besides, the protection provided through platelet aggregation inhibition, the bioactive molecules present in the spices and nuts also protect from various cardio-metabolic risk factors[8].

METHODOLOGY

In view of this, online literature search was conducted using the keywords for example, platelet aggregation, anti-platelet, anti-thrombotic, inhibition, activation, thrombosis, *in vitro, in vivo* combining with common as well as botanical names of various spices, condiments and nuts on the databases namely, Pubmed, Springer Link, Scopus, Science Direct, Google Scholar, and Research gate to find out the studies carried out on this aspect. Finally, the major findings of all the relevant papers selected for this review article is presented in following sections under the two separate headings; platelet aggregation inhibition activity of spices and condiments and nuts.

Platelet aggregation inhibition activity of spices and condiments

Wang *et al*.[9] reported that capsaicin; a bioactive compound of chilli peppers (*Capsicum frutescens;* Family - Solanaceae) effectively inhibits platelet aggregation induced by thrombin and collagen. However, marginal inhibition was observed on rat platelet aggregation induced by arachidonic acid (AA) and calcium ionophore A23187. An IC_{50} value of 85 µg/ml was found for collagen-induced platelet aggregation.

The anti-platelet activity of nutmeg (*Myristica fragrans;* Family - Myristicaceae) on rabbit platelets was investigated by Rasheed *et al*.[10]. Eugenol and isoeugenol were the two most active components found in nutmeg oil. Indomethacin was taken as a reference drug and platelet aggregation was induced by arachidonic acid. At the same concentration, indomethacin 1 µg/mL was substantially more effective than eugenol, whereas eugenol at a concentration of 1 µg/mL and 10 µg/mL showed a dose-response relationship ($P< 0.05$). Additionally, the pure oils demonstrated inhibitory efficacy against AA-induced aggregations, with an IC_{50} of around 10 µg/mL. Interestingly, recently the effects of *Myristica fragrans* ethanol extract (MF) on sepsis and sepsis-associated thrombocytopenia (SAT) have been studied by Jeong *et al*.[11] using flow cytometry, desialylation and activation of platelets treated with sialidase and adenosine diphosphate (a platelet agonist). Through the inhibition of bacterial sialidase activity in washed platelets, the extract inhibited platelet desialylation and activation. Furthermore, in a mouse model of sepsis generated by cecal ligation and puncture, MF decreased inflammation, enhanced survival, and decreased organ damage. By suppressing circulation sialidase activity, it also stopped platelet desialylation and activation while preserving platelet numbers. Hepatic JAK2/STAT3 phosphorylation and thrombopoietin mRNA expression are decreased when platelet desialylation is inhibited. This decreases hepatic Ashwell–Morell receptor–mediated platelet clearance. The study provides insight into sialidase-inhibition-based sepsis therapy approaches and paves the way for the creation of plant-derived medicines for SAT and sepsis.

According to Srivastava[12], ether extract of Carom seeds (*Trachyspermum ammi*; Family- Apiaceae) inhibited platelet aggregation in a concentration-dependent manner when induced with arachidonic acid (AA), epinephrine, and collagen. It worked best against aggregation induced by AA. It inhibited AA-induced aggregation in every blood sample at a concentration of > 60 µg/ml. At 100–200 µg/ml concentration, the second phase of epinephrine-induced aggregation was eliminated. However, relatively higher concentration (400 µg/ml) was required to prevent collagen-induced aggregation.

The anti-platelet property of Cumin (*Cuminum cyminum;* Family - Apiaceae) and Turmeric (*Curcuma longa;* Family - Zingiberaceae) were investigated by Srivastava[13]. Ether extracts of Turmeric and Cumin inhibited aggregation induced by arachidonic acid and 137 ± 37 µg/mL and 92 ± 73 µg/mL were the doses of platelet-rich plasma (PRP) that abolished the AA-induced aggregation by turmeric and cumin extracts, respectively. The two spice extracts were unable to inhibit collagen and calcium ionophore A23187 induced platelet aggregation and a significantly higher concentration was required for slight reduction in adenosine diphosphate (ADP)-induced aggregation. Interestingly, Ar-turmerone, an active constituent from the rhizome of *Curcuma longa* (Family- Zingiberaceae) has shown platelet aggregation inhibition property. It effectively inhibited platelet aggregation caused by arachidonic acid (IC_{50}, 43.6 µM) and collagen (IC_{50}, 14.4 µM) without any impact on the platelet aggregation caused by thrombin. Moreover, as compared to aspirin, Ar-turmerone was more potent platelet inhibitor against collagen-induced platelet aggregation[14].

Shah *et al*.[15] studied the platelet aggregation inhibitory effect of curcumin, extracted from turmeric. The platelet agonists arachidonic acid (AA; 0.75 mM), collagen (20 mg/mL), platelet-activating factor (PAF; 800 nM), epinephrine (200 µM), and ADP (4 µM) were used to induce platelet aggregation. The curcumin was found effective against PAF and AA with IC_{50} values of 25 and 30 mM, respectively, while higher concentration of curcumin was required to inhibit aggregation brought on by other platelet agonists. When curcumin was pre-treated with platelets, platelet aggregation caused by the calcium ionophore A23187 was inhibited (IC_{50}; 100 µM). However, aggregation caused by the protein kinase C (PKC) activator phorbol myrsitate acetate (1 µM) was not inhibited by curcumin up to a concentration of 250 µM. By utilising fura-2 acetoxymethyl ester, curcumin (100 µM) reduced the intracellular Ca^{2+} mobilisation produced by A23187. Moreover, curcumin also inhibited platelets from producing thromboxane A2 (IC_{50}; 70 µM).

Srivastava[16] demonstrated platelet aggregation inhibitory activity of two active compounds, eugenol and acetyl eugenol isolated from the oil of cloves (*Syzygium aromaticum;* Family - Myrtaceae). Eugenol and acetyl eugenol were shown to be more effective than aspirin in suppressing platelet aggregation caused by arachidonate, adrenaline, and collagen based on their

IC_{50} values. Eugenol inhibited platelet aggregation induced by AA, collagen and adrenaline with IC_{50} values of 0.8 ± 0.1 µM, 39 ± 11 µM, and 12 ± 3 µM, while acetyl eugenol inhibited aggregation of platelets with IC_{50} values of 2 ± 0.6 µM, 56 ± 27 µM and 11 ± 2 µM, respectively. The standard anti-platelet drug aspirin demonstrated the IC_{50} values as 28 ± 22 µM, 74 ± 28 µM and 50 ± 13µM against AA, collagen and adrenaline respectively.

Guh *et al*.[17] evaluated *in vitro* anti-platelet activity of gingerol, a bioactive component of *Zingiber officinale* (Family-Zingiberaceae) against different agonists inducing washed platelets from rabbit blood. Platelet aggregation produced by collagen and ADP was inhibited by gingerol at concentrations ranging from 0.5 to 20µM. Gingerol also decreased the production of prostaglandins D2 and TXB2 by Arachidonic acid at doses of 0.5–10µM. Interestingly, Ginger has also shown *in vivo* anti-platelet activity against ADP- and epinephrine-induced platelet aggregation after administration of its single dose (10 g) to CAD patients[18].

The *in vitro* platelet aggregation inhibitory action of aqueous extract of Cardamom (*Elettaria cardamomum*; Family - Zingiberaceae) on human platelets was investigated by Suneetha and Krishnakantha[19]. Epinephrine (2.5 mM), ADP (2.5 mM), calcium ionophore A 23187 (6 mM), collagen (10 mM), and ristocetin (1.25 mg/mL) were among the agonists used to stimulate human platelets. With epinephrine, ADP, calcium ionophore A 23187 and collagen, the IC_{50} values were 0.21, 0.49, 0.59 and 0.55 mg, respectively, and there was no platelet aggregation inhibition observed with ristocetin. At IC_{50}, the inhibitory effect was dose-dependent and time-dependent, with values varying from 0.14 to 0.70 mg.

Administration of 2.5 g Fenugreek powder (*Trigonella foenum-graecum*; Family - Fabaceae) twice daily to healthy individuals for 3 months did not affect platelet aggregation inhibition[18].

Jessie and Krishnakantha[20] investigated the inhibitory effect of aqueous extract of saffron (*Crocus sativus;* Family - Iridaceae) on human platelets. Collagen (11 mg/mL), epinephrine (76 µM), ADP (61 µM), calcium ionophore A23187 (6 µM), and ristocetin (1.25 mg/mL) were used to stimulate human platelets in the presence and absence of saffron extract. The IC_{50} values for these agonists were 0.86, 0.35, 0.66, and 0.59 mg, respectively, and ristocetin showed no inhibition. Moreover, the inhibitory impact was time-dependent and dose-dependent, with values ranging from 0.16 to 0.80 mg.

Suneetha and Krishnakantha[21] examined the antiplatelet aggregation activity of aqueous extracts of curry leaf *Murraya koenigii* (Family- Rutaceae) and coriander leaf *Coriandrum sativum* (Family - Apiaceae) against human platelets using agonists such as adenosine diphosphate, epinephrine and collagen. After one minute of incubation, the IC_{50} values for platelet aggregation inhibition were found as 0.94 ± 0.049, 0.65 ± 0.042 and 0.58 ± 0.035 mg/mL for curry leaf and 0.55 ± 0.045, 0.66 ± 0.033 and 0.57 ± 0.031 mg/mL for coriander leaf with ADP, epinephrine, and collagen, respectively.

Park *et al*.[22] investigated the inhibitory effects of four acidamides, namely, were piperine, pipernonaline, piperoctadecalidine, and piperlongumine that were extracted from the fruits of *Piper longum* L. (Family - Piperaceae). Except the thrombin-induced aggregation, all four of the tested acidamides shown dose-dependent inhibitory effects on washed rabbit platelet aggregation induced by collagen, arachidonic acid, and platelet-activating factor (PAF). Piperlongumine demonstrated more potent inhibition of rabbit platelet aggregation produced by collagen, AA, and PAF compared to other acidamides. At the concentration of 300, 150, 30, and 10 mM, piperlongumine showed 100%, 100%, 49.8%, and 19.9% inhibitory effects on collagen induced platelet aggregation, respectively. Piperlongumine also exhibited 100%, 76.4%, and 12% inhibitory effects, respectively, at 300, 150, and 30 mM concentrations in an AA induced test as well as 100%, 100%, and 29.9% inhibition against PAF-induced platelet aggregation, respectively.

Piperine; an active molecule from *Piper nigrum* and *Piper longum* has also shown anti-platelet effects. Son *et al*.[23] have shown the mechanism behind anti-platelet action of piperine using Rabbit platelets and murine macrophage RAW264.7 cells. It was observed that piperine was able to significantly inhibit the liberation of AA liberation through diminishing $cPLA_2$ activity in collagen-stimulated platelets. Moreover, a significant inhibition of the activity of TXA_2 synthase, but not of COX-1, in platelets was also observed indicating that platelet aggregation was inhibited through attenuation of $cPLA_2$ and TXA_2 synthase activities by piperine, instead of through the inhibition of COX-1 activity. On the other hand, a significant suppression of lipopolysaccharide-induced generation of prostaglandin (PG) E_2 and PGD_2 in RAW264.7 cells was executed by piperin through inhibiting the activity of COX-2, without any effect on $cPLA_2$.

Jantan *et al*.[24] investigated platelet aggregation inhibitory activity of different phytoconstituents from Zingiberaceae family. Arachidonic acid, collagen and adenosine diphosphate were taken to induce platelet aggregation in human whole blood and aspirin was taken as a positive control. IC_{50} values of less than 84 µM were found for curcumin from *Curcuma aromatica*, cardamonin, pinocembrine, 5, 6-dehydrokawain from *Alpinia mutica*, and 3-deacetylcrotepoxide from *Kaempferia rotunda* when platelet aggregation was induced by AA. Curcumin was shown to be the most effective anti-platelet agent, with IC_{50} values of 37.5, 60.9, and 45.7 µM, against AA-, collagen-, and ADP-induced platelet aggregation, respectively.

In vitro human anti-platelet aggregation potential of active principles of various spices, such as,eugenol, capsaicin, piperine, quercetin, curcumin, cinnamaldehyde, and allyl sulphide, was demonstrated by Raghavendra and Naidu[25]. Various agonists were used *viz*., collagen (500mg/mL), ADP (50 µM), calcium ionophore A-23187 (20 µM) and arachidonic acid (1.0mM) to induce platelet aggregation. The most effective inhibitors of AA-induced platelet aggregation among the active principles examined were capsaicin and eugenol, with IC_{50} values of 14.6 µM and 0.5 µM, respectively and

eugenol was 29 times more effective than aspirin in inhibiting AA-induced human platelet aggregation.

Kim *et al.*[26] reported the anti-platelet activity of several phytocompounds isolated from *Cinnamomum cassia* (Family - Lauraceae) extract. The platelet aggregation induced by arachidonic acid was inhibited by coniferaldehyde, eugenol, cinnamic alcohol, amygdalactone, 2-methoxycinnamaldehyde, and 2-hydroxycinnamaldehyde with the values of 0.82, 3.8, 31.2, 5.16, 16.9 and 40.0 μM, respectively. Moreover, acetylsalicylic acid (reference drug) had an IC_{50} value of 60.3μM. Furthermore, epinephrine-induced platelet aggregation was inhibited with eugenol, cinnamic alcohol, amygdalactone, cinnamaldehyde, 2-methoxycinnamaldehyde, 2-hydroxycinnamaldehyde, and coniferaldehyde with IC_{50} values of 1.86, 37.7, 1.10, 25.0, 15.3, 16.8, and 0.57 μM, respectively as compared to acetylsalicylic acid (IC_{50} 50.0 μM). It was observed that the two most potent anti-platelet components of *C. cassia* were eugenol and coniferaldehyde.

Ro *et al*.[27] evaluated *in vitro* platelet aggregation inhibitory activity of onion (*Allium cepa*; Family - Amaryllidaceae) peel extract (OPE) on collagen-induced washed rat platelets. Quercetin, was found as an active component through HPLC analysis of OPE. The IC_{50} value for quercetin was found 65 μg/mL in collagen (5 μg/mL)-induced platelet aggregation.

González *et al*.[28] evaluated *in vivo* anti-platelet aggregation effect of aqueous extract of garlic (*Allium sativum*; Family - Amaryllidaceae) using various agonists such as collagen, arachidonic acid, adenosine diphosphate, and epinephrine. There were significant differences in platelet activation in response to every agonist ($P<0.05$). Arachidonic acid had the most promising anti-platelet effect, whereas a combination of collagen and arachidonic acid had the least.

Platelet aggregation inhibition activity of Nuts

Ghayur *et al*.[29] reported the anti-platelet activity of aqueous-methanol (70%) extract of betel nut (*Areca catechu;* Family - Arecaceae) in human platelet-rich plasma. Platelet aggregation was induced by different agonists such as adenosine diphosphate, arachidonic acid, epinephrine, platelet-activating factor (PAF) and Ca^{2+} ionophore. *A. catechu* crude extract (Ac.Cr) inhibited platelet aggregatory effect of various agonists in a dose-dependent fashion (0.07 to 2 mg/mL). Ac.Cr had shown the most significant inhibitory effect against Ca^{2+} ionophore and ADP-induced aggregation. The IC_{50} values were found 0.628, 1.590, 1.677, 1.902 and 0.987mg/mL for ADP, AA, epinephrine, PAF and Ca^{2+} ionophore, respectively. Moreover, acetylsalicylic acid, a reference agent revealed an IC_{50} value of 0.03mg/mL against AA-induced platelet aggregation.

Shanmuganayagam *et al*.[30] analysed *in vitro* anti-platelet activity of different phenolic fractions of seed and skin of grape (*Vitis vinifera;* Family - Vitaceae), unfractionated grape skin (GSK) and gallic acid. Dried fruits of *V. vinifera* are well known as Raisins and consumed especially in sweet dishes. Six GSK phenolic fractions were sequentially prepared with water (fraction 1), 50% water/ethanol (fraction 2), ethanol (fraction 3), 50% ethanol/methanol (fraction 4), methanol (fraction 5), and 80% aqueous acetone (fraction 6). Surprisingly, the collagen-induced platelet aggregation was enhanced by fractions 1, 2, and 3 by 3.8 ± 1.4% ($p< 0.05$), 7.2 ± 2.4% ($p< 0.05$), and 23.8 ± 4.2% ($p< 0.001$), respectively, whereas, platelet aggregation was considerably decreased by fractions 4, 5, and 6 by 48.4 ± 11.4% ($p< 0.005$), 89.6 ± 5.3% ($p< 0.001$), and 72.5 ± 8.3% ($p< 0.001$), respectively. Notably, fractions, 4-6 were enriched in polygalloyl polyflavan-3-ols. However, gallic acid showed no discernible impact, whereas unfractionated GSK exhibited slight decrease of platelet aggregation (12.0 ± 3.8%).

Park *et al*.[31] reported the anti-platelet activity of methanolic extract of *Pistacia chinensis* (Family - Anacardiaceae) bark in rat platelets induced by ADP under *in vitro* conditions. The plant extract inhibited the platelet aggregation in a concentration ranging from 2.5-20 μg/mL. Moreover, it also reduced the [Ca(2+)] i, ATP, and TXA2 release in ADP-activated platelets, but also enhanced cAMP production in resting platelets. This could be suggested that the other plant of the same family and genus, *Pistacia vera* may also possess anti-platelet activity and needs scientific investigations.

Meshkini and Tahmasbi[32] evaluated *in vitro* platelet anti-aggregation effects of hull extract of Walnuts (*Juglans regia*; Family - Juglandaceae). The wall hull extract inhibited thrombin-induced platelet aggregation by 50% at a concentration of 50 μg/mL and exhibited a dose-dependent action on platelet aggregation without causing any cytotoxic effects on platelets.

Rehman *et al*.[33] evaluated the impact of Chilgoza Pine (*Pinus gerardiana*; Family - Pinaceae) nut oil (PGNC) on *in vitro* platelet aggregation after activation induced by collagen and adrenaline. Platelet-rich plasma (PRP) was treated with 10μl PGNC, and the greatest impact was observed. When collagen was used to activate platelets, PGNC significantly ($p<0.001$) lengthened the time it takes for platelets to aggregate in a dose-dependent manner. On the other hand, when triggered by epinephrine, PGNC reduced the time for platelet aggregation in a concentration dependent manner significantly ($p<0.001$).

Baru (*Dipteryx alata;* Family - Fabaceae) is a nutritious nut from central-western area of the Brazilian Savanna; especially rich in tocopherols. The effect of Baru almond oil supplementation on vascular function, thrombus formation and platelet aggregation in the aorta arteries of Wistar rats was investigated by Silva-Luis *et al*.[34]. Both platelet aggregation and the generation of the superoxide anion radicals were significantly diminished ($p<0.05$) by Baru oil supplementation. Furthermore, vascular function of the aorta arteries was significantly ($p<0.05$) enhanced and antithrombotic effect was also observed with supplementation of Baru oil.

Interestingly, active constituents of some of the nuts have shown promising anti-platelet activity. For example, Morin hydrate; a flavonol which is an important constituent of Almonds (*Prunus dulcis*; Family – Rosaceae) has effectively

inhibited collagen (3 µg/ml) - and thrombin (0.05 U/ml)-induced human platelet aggregation in a dose-dependent manner. The IC_{50} value obtained against collagen-induced aggregation was 50 µM. The study further reported that the mechanism behind anti-platelet activity of morin hydrate is through down-regulation of TXA_2 production and integrin $\alpha_{IIb}\beta_3$ activation, as well as by upregulation of cAMP generation[35].

Despite this, there are some of the spices namely, asafoetida, star anise, cinnamon and nuts such as cashew nut, macadamia nut, hazel nut and apricot whose platelet aggregation inhibition activity could also be scientifically evaluated in order to know their health benefits in prevention of cardiovascular diseases.

CONCLUSION

Coronary heart disease and stroke are leading causes of mortality and morbidity in the human population. Platelet aggregation is one of the bases behind beginning of these athero-thrombotic events. Synthetic anti-platelet drugs are available but these are associated with adverse effects. Therefore, plant based anti-platelet drugs provides hope. Several of the nuts and spices possess significant anti-platelet activity. Moreover, these are enriched with therapeutic bioactive molecules which provide additional beneficial properties for example, antioxidant, anti-inflammatory, hypotensive, hypolipidemic, thrombolytic etc. Dietary consumption of these could be therefore, helpful in prevention of cardiovascular diseases. However, long term scientific studies are warranted to validate this.

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