

Traditionally Used Plants with the Inhibitory Effect of Platelet Aggregation

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Author's Contribution

All the authors contributed significantly to the research that resulted in the submitted manuscript.

Article info.

Received: September 12, 2018

Accepted: November 16, 2018

Funding Source: Nil

Conflict of Interest: Nil

Cite this article: Akram Z, Hussain M, Noreen A, Razzak M, Ibrahim S. Traditionally Used Plants with the Inhibitory Effect of Platelet Aggregation. *RADS J. Pharm. Pharm. Sci.* 2018; 6(3): 200-207.

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ABSTRACT

During hemostasis, after vascular injury and wound healing process, platelets play a very significant role, where the platelets hypersensitivity is also related to the progression or development of various cardiovascular diseases. In this regard, there is a need to find such compounds, which provide more potent and safer activity against platelets with minimum side effects. This review article provided an overview of various medicinal plants having antiplatelet properties or pointed out the constituents associated with the activity, the part used for the isolation of plant constituents, and different pathways which mediate the antiplatelet activity. In this review different classes such as Liliaceae, Zingiberaceae, Rutaceae, Arecaceae and Asteraceae were suggested for their antiplatelet properties to which various medicinal plants belong possessing such properties. Specific bioactive components in different medicinal plants which relate to the antiplatelet properties are flavonoids, polyphenols, terpenoids and glucosides. These substances correct the abnormal state of platelets causing various diseases by changing the signaling pathways such as inhibition of thromboxane production, reduction of PKC activator; reduce the intracellular level of calcium, PAF or collagen receptor antagonist and inhibition of PLC and GPIIb-IIIa activation. It was observed that most of the components in these plants inhibiting the platelet activity by inhibiting ADP, Thromboxane and PAF activity. These investigated mechanisms provided data to develop new formulation in the treatment of thromboembolic disorders by inhibiting the aggregation of platelets.

Keywords: Hemostasis, cardiovascular, thromboxane, PKC activator.

INTRODUCTION

Among the different health-related issues cardiovascular diseases (mainly stroke and coronary heart disease) are the major cause of death around the world. According to the WHO 17.5 million deaths related to cardiovascular disease (CVD) were reported in 2012 [1]. In Low and Middle-income countries the ratio of death occurred from CVD is more than 80% [2]. In low income countries, the

researcher revealed that by 2030, CVD will be more responsible for death than infectious diseases [3]. Platelets play an important role during the process of hemostasis and wound healing [4]. Meanwhile, many complications cause because of their hyper sensitivity involved in the augmentation of several CVD such as peripheral artery disease, atherosclerosis, thrombosis, ischemic stroke, and myocardial infarction [5-9]. Obesity, smoking, hypercholesterolemia, stress and diabetes mellitus

are the different risk factors of CVD which are associated to hyperactivity of platelets [10]. Platelet adherence to the receptor of sub-endothelial matrix after the injury of blood vessels / erosion of atherosclerotic plaque triggers platelets activation and aggregation [11, 12]. Thromboxane A₂, ADP (adenosine diphosphate), serotonin, P-Selectin, Ca²⁺, and fibrinogen, are the different prothrombotic mediators released by the activated platelets following thrombus formation [12]. An artery circulating blood to different vital organs such as the brain or heart having a thrombus is the leading cause of angina and myocardial infarction [13]. So protection must be provided against CVD by inhibiting the platelet aggregation affecting millions of people worldwide. Different antiplatelet drugs are clinically used to prevent angina, stroke and acute coronary syndromes such as commonly used aspirin and clopidogrel while others administered are ticlopidine, abciximab, tirofiban and eptifibatide) [14, 15]. Currently clinically used medicines have limited actions accompanied by significant side effects such as gastric ulcer, hemorrhage, and risk for the reoccurrence of cardiovascular events as well as developed resistance against the therapy [16-20]. In this concern, different agents are still in research concerns worldwide for the origin of more potent and safer antiplatelet drug.

In traditional medicine different medicinal plants have been used historically to treat various kinds of diseases. For this purpose, World Health Organization (WHO) encourages scientist to inculcate conventional plants, to get new pharmacologically active agents accompanying least side effects. Through different articles it has been revealed, that high fruit and vegetable consumption may prevent CVD *via* inhibiting the platelets functioning [21-23].

This article includes apotheosis of traditional plants used for antiplatelet activity studies *via* research experiments available through literature. Particular attention in this review is focused on parts of the plant used for antiplatelet activity and specific mechanism of antiplatelet action.

ANTIPLATELET ACTIVITIES OF MEDICINAL PLANTS

The article provides and compiles the data in summarized form on medicinal plants having antiplatelet activity agents, which includes plant

name, its family, parts responsible for activity, doses and active principles.

***Allium cepa* (Liliaceae)**

Peel extract of *A. cepa* (Onion) in rats revealed platelet aggregation inhibition induced by collagen and the value of IC₅₀ is 80.0 µg/ml. Quercetin isolated from the peel extract of onion is considered that may be it is the agent responsible for producing an antiplatelet effect by up-regulation of cAMP levels and down-regulating thromboxane A₂ *via* reducing the activities of calcium ions, TXA₂ (Thromboxane A) and COX-1 (cyclooxygenase-1) synthase [24]. Different mechanisms for an antiplatelet activity of onion extract observed through other studies, manifested reduction of Arachidonic acid (AA), inhibition of TXA₂ synthase and the blockade of PGH₂/TXA₂ [25]. Flavonol glucosides components of *A. cepa* showed the inhibition of collagen-induced platelet aggregation using rat PRP (platelet-rich plasma). It was found that the extracted compounds, such as quercetin function as a potent inhibitor for platelet aggregation than quercetin glucosides, whereas quercetin glucosides performed high antioxidant activities [26].

***Allium sativum* (Liliaceae)**

Garlic (*A. sativum*) administered as garlic oil in healthy volunteers along with coronary artery disease patients showed inhibited platelet aggregation in *ex vivo* study [27]. Another study showed that *A. sativum* (alcoholic extract) in a dose-dependent manner inhibition of platelet aggregation took place by inhibition of ADP induced human platelet aggregation [28]. Other investigations revealed that active compounds like ajoene, allicin and thiosulphinates, exhibited antiplatelet activity [29-31], and mechanisms related to this activity are decreased intracellular calcium level [32], AA metabolism alteration [31] and *via* inhibiting the secretion of platelets [33], besides, ajone inhibits fibrinogen and von Willebrand factor (vWF) for binding to its receptors which are GPIIb/IIIa [34].

***Allium ursinum* (Liliaceae)**

A. ursinum owes high potential for CVD prevention and treatment and the ethanolic extract obtained by the leaves signified ADP induced inhibition of platelet aggregation and mechanism involved was similar to that of clopidogrel [28]. Another investigation has shown that two flavonoid glycosides, 3-O-β-

neohesperidoside and Kaempferol 3-O- β -neohesperidoside-7-O- β -D-glucopyranoside present in *A. ursinum* leaves collagen induced human platelet aggregation inhibition in the *in-vitro* study [35].

***Arbutus unedo* (Ericaceae)**

In oriental Morocco *A. unedo* (Strawberry) is used to treat arterial hypertension [36]. The crude aqueous extract of diethyl ether or ethyl acetated *A. unedo* at different concentration (0.015 – 1.5mg/ml) exhibited reduced platelet aggregation generated by thrombin and also performed an activity regarding the potent ROS scavenger. With this extract washed platelets were also treated which did not show any alteration in thrombin evoked the release of calcium from intracellular storage, where as it decreases the entry of calcium induced by thrombin or selectively depletion of two stored calcium within the platelet and the dense tubular system [37]. Moreover, methanolic extracted isolated tannins of *A. unedo* exhibited strong antiplatelet activity in rats platelets [38]. Another data indicated dose-dependent induced platelet aggregation by an extract of strawberry in the concentration of 0.1 – 1mg/ml inhibiting Adenosine diphosphate (ADP). It also inhibited inflammatory platelet mediators in atherosclerosis such as P-selection, RANTES (Regulated on Activation Normal T Cell Expressed and Secreted), sCD40L and IL-1 β [39].

***Areca catechu* (Arecaceae)**

Crude extract of *A. catechu* inhibited the ADP, A.A, epinephrine, platelet aggregating factor (PAF), or calcium-ionophore induced platelet aggregation. A significantly potent effect was observed when calcium-ionophore and ADP was used as agonist [40]. Isolated catechol from the extract of *areca nut* showed antiplatelet as well as anti-inflammatory activities, mediated *via* inhibiting TXA₂ production, COX pathway and reactive oxygen species (ROS). This antiplatelet effect of catechol was analyzed persistently by *ex vivo* studies [41].

***Conyza canadensis* (Asteraceae)**

Pretreatment of platelet with the extract of *C. canadensis* inhibited the ADP induces platelet aggregation. Further, it inhibited the nitration and oxidation of proteins within the blood platelets. It is consider that may be the radical scavenger activity is the part which relates to its antiplatelet effect [42].

Another study showed that aqueous extract of *C. canadensis* in the concentration of 0.75mg/ml inhibited collagen induce platelet aggregation and relate this activity with the polysaccharide part of the aqueous extract which may be performing this antiplatelet effect [43].

***Curcuma amada* (Zingiberaceae)**

The chloroform extract obtained from the mango ginger rhizome yield amadaldehyde which inhibited the ADP induced platelet aggregation and IC₅₀ value of this inhibition is 113 μ g [44].

***Curcuma wenyujin* (Zingiberaceae)**

This medicinal plant yields several pharmacological properties [45]. It has been reported that an isolated component of curdione from the essential of this plant inhibited thrombin and PAF induced aggregation of platelets in an *in-vitro* study with 60 μ M-80 μ M IC₅₀ value of platelet inhibition. Furthermore, curdione decreases P-selection expression in Platelets activated by PAF. The mechanism involved in platelet inhibitory activity by curdione may be due to increased cAMP level or inhibition of intracellular calcium mobilization [46].

***Curcuma longa* (Zingiberaceae)**

C. longa L. medicinal plant has anti-atherosclerosis, anticancer, antidiabetic and antioxidant pharmacological activities. Biologically active components of *C. longa* reported are curcuminoids which inhibit rats *in vitro* platelet aggregation in a dose-dependent manner. Multiple mechanisms are related to this inhibition such as decreased TXA₂ increased nitric oxide level and reduced 12-lipoxygenase activity in platelets [47].

***Feroniella lucida* (Rutaceae)**

Coumarine Feroniellin B isolated from *F. lucida* roots inhibited ADP induced human platelet aggregation with IC₅₀ value of 0.287mM [48], so due to this inhibitory effect, it is used in CVD remedy.

***Ginkgo biloba* (Ginkgoaceae)**

The extract of *G. biloba* inhibited dose-dependent platelet aggregation induced by ADP and collagen. This plant also inhibited the production of TXA₂ and augmented the level of cAMP in platelet which reduced intracellular calcium level of platelets during the incubation of platelets. Flavonoids or ginkgo

glides may perform this antiplatelet effect obtained from the extract of *G. biloba* [49]. *Ex vivo* study has shown platelet aggregation at a small dose of ticlopidine (50mg/kg/day) in combination with the (40mg/kg/day) dose of *G. biloba* extract (EGb 761) [50] induced by ADP. Another *in vitro* study showed that usage of cilostazol and *G. biloba* extract in human platelets resulted in augmented inhibition of induced, shear and collagen platelets inhibition as compared to each drug alone [51].

***Houttuynia cordata* (Saururaceae)**

Becatamide isolated from *H. cordata*, reduced platelet aggregation by suppressed expression of P-selectin, cyclooxygenase enzymes inhibition, and TXB₂ production which have a potential to treat or prevent platelet activation related disorders [52].

***Humulus lupulus* (Cannabaceae)**

Xanthohumol obtained from the extract of *H. lupulus* L., having strong inhibition effect of platelet aggregation on wash human platelets induced by collagen. The mechanism which exhibited the antiplatelet activity may be due to the results of PI3-kinase inhibition and PLC γ 2-PKC cascade inhibition, which further leads towards the decreased production of TXA₂ and calcium mobilization [53]. Another study showed that the extract also reduced ONOO- related lipid peroxidation of platelet [54].

***Ilex pubescens* (Aquifoliaceae)**

2-(trans-caffeoyloxy)methyl-3-hydroxy-1-butene-4-O-beta-Dglucopyranoside and 2-hydroxymethyl-3-caffeoyloxy-1-butene-4-O-beta-D-glucopyranoside are the 2 hemiterpene glucosides isolated from *I. pubescens* roots exhibited potent antiplatelet effect [55]. Another study has been shown that the active Ilexonin A, isolated from *I. pubescens* had antiplatelet activity augmenting the cAMP level. It also revealed that platelet phosphodiesterase inhibitory effect through Ilexonin A was more potent as compared to verapamil [56].

***Laurus nobilis* (Lauraceae)**

Cinnamtannin B-1, isolated from *L. nobilis* extract indicated that it has a biological property which changes platelet aggregation properties [57]. Cinnamtannin B-1 reduces platelet aggregation of human platelet by inhibiting tubulin reorganization induced by thrombin [58]. A study has also shown

that in platelets taken from diabetes patient had Cinnamtannin B-1 exerted an antioxidant activity and decreased calcium mobilization and hyper aggregability [59].

***Magnolia obovata* (Magnoliaceae)**

Biphenolic component of *M. obovata* leave extract, Obovatol exhibited collagen induced-antiplatelet activity at 1-10 μ M concentration in *ex vivo* study induced and reduced platelet aggregation activity effected by collagen and A₁ in rabbits during *in vitro* study with the IC₅₀ value of 2.4 \pm 0.8-4.8 \pm 0.9 μ M. The mechanism at which Obovatol exerted antiplatelet effect may be through the inhibition of PLC- γ ₂ phosphorylation [60].

***Mauritia flexuosa* (Arecaceae)**

M. flexuosa oil extract in 0.1-1mg/ml concentration inhibited dose-dependent platelet aggregation and secretion, by ADP, collagen and thrombin receptor activator (peptide-6). It reduced the release of sP-selectin from platelets at the same concentration, which is an atherosclerotic-related inflammation mediator [61].

***Paullinia cupana* (Sapindaceae)**

Guarana herb is used mostly in soft drinks in Native to Latin American countries. *P. cupana* aqueous extract exerted antiplatelet effect in rabbits and AA or ADP induced human platelet aggregation [62]. Further caffeine and catechins obtained from guarana seed extract also inhibited platelet aggregation [63]. Further studies revealed that *P. cupana* aqueous extract at 100mg/ml concentration reduced the platelets aggregation related to the activity of decreased production of thromboxane [64].

***Vitis labrusca* (Vitaceae)**

Leaf extract obtained from the *V. labrusca* inhibited the platelet aggregation of incubated platelets induced by ADP. Chemical analysis revealed that quercetin, isorhamnetin, and rutin present in the extract of *V. labrusca* leave exhibited antiplatelet activity. The TXB₂ inhibition and inhibition of serotonin secretion mechanism is responsible for this effect [65].

***Vitis vinifera* (Vitaceae)**

Polyphenolic fractions isolated from skin and seed of grapes have revealed inhibited aggregation of platelet

and low-density lipoprotein oxidation during *in vitro* study [66]. It also showed that seed of grapes at 5-100µg/ml decreased the oxidative stress of platelets, which showed a more potent effect than resveratrol solution [67].

Zingiber officinale (Zingiberaceae)

Medicinal plant of *Z. officinale* has vast therapeutic uses such as antidiarrheal, stomachic, expectorant, antiasthmatic, cardiogenic and hemostatic. A considerable amount of investigation has been done on the effect of ginger and its components on the functions of platelets [68-71]. One study reported that the *Z. officinale* rhizome inhibited collagen, ADP, AA, Epinephrine dependent aggregation of platelets [72]. An active component of ginger (gingerol) in 0.5-20µM concentration inhibited the aggregation of platelet-induced by collagen and ADP. At 0.5-10µM concentration gingerol inhibited the prostaglandins D₂ and TXB₂ formation by Arachidonic acid [73] related to inhibition of thromboxane production. Further studies also revealed that gingerol and shogaol isolated from *Z. officinale* rhizomes retained potent antiplatelet activity [74].

DISCUSSION

Medicinal plants are considered as natural remedies commonly used for prevention or treatment of various disorders, such as CVD, mostly in those developing countries where either the services are limited or modern medical health resources are meager [75, 76]. Those herbs and plants which have the beneficial properties for cardiovascular diseases are mainly related to the antiplatelet and vasorelaxant activities to fulfill cardioprotective properties. This review indicated that various plants and herbs are evaluated for the antiplatelet activities worldwide and most studied families to which those plants belong are Liliaceae, Zingiberaceae, Rutaceae, Arecaceae and Asteraceae. Most of the plants evaluated for antiplatelet properties showed its activity in its extract form while some of the plants have been reported with their bioactive components individually responsible for the antiplatelet activity. *In vitro* and *in vivo* investigations have been reported on the platelets of rats, rabbits and human in the form of platelet-rich plasma, washed platelets and whole blood samples. Most of the plants have been investigated against the inducers of ADP, collagen, and AA. The mostly mechanism at which these plants

are performing their antiplatelet activities are; inhibition of thromboxane production, reduction of PKC activator, suppresses the cytoplasmic increases of calcium, PAF or collagen receptor antagonist and inhibition of PLC and GPIIb-IIIa activation. A recent work performed by Izzo mentioned that remedies in form of herbal plants are best tolerated than those medications which are synthetically developed [77]. So there is need to carefully investigate different herbal plants already identified with their antiplatelet activity for sensitive situations like pediatric and pregnancy.

CONCLUSION

Globally, especially in the developing countries, one of the leading causes of death is cardiovascular diseases. Most articles in this review provided evidence for different plants for antiplatelet property in case of thrombotic disorders. Most of the newly identified compounds isolated from the extract of plants showed antiplatelet activity either equivalent or more potent than the already identified agents and clinically used drugs. These knowledge and data provided a chance to pharmaceutical companies to approach different strategies, which enhance the cardiovascular health and decrease the cardiac-related issues through elucidating the side effects of currently available therapies.

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