Review Article

A Review of Medicinal Herbs Capable of Preventing Blood Coagulation and Platelet Aggregation

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Abstract

Blood coagulation is a process carried out to prevent blood loss when a person is wounded. The blood coagulates in the wound place and creates a barrier which prevents bleeding. The blood coagulation process is one of the most important and vital physiological processes in the human body which is affected by many factors. Many congenital and acquired defects in each of these factors can affect the coagulation process and cause many problems for humans. Related articles were searched from Google Scholar, PubMed, Science Direct, High Wire, MD Consult and Scopus data bases, and finally 19 articles were included in this study. In this study, 19 anti-coagulant medicinal plants were diagnosed and evaluated. Finally, it follows from this study that there are many medicinal herbs that have different effective substances to prevent blood coagulation by various mechanisms. These plants can be used as highly efficient resources in the production of valuable drugs against diseases caused by blood coagulation.

Keywords: Medicinal plants, coagulation, coagulation factors

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Introduction

Blood coagulation is a process for preventing blood loss during bleeding caused by wounds. The blood coagulates in the wound place and creates a barrier which prevents bleeding. Even when the blood is exiting from the vessels in the body, it coagulates (1, 2). The coagulation procedure involves the formation of a clot which is separated from the blood fluid that is called serum in that state (3). The blood coagulation system begins with the activation of factor XII or VII or both. They activate the thrombin protein (4). The thrombin directly breaks peptide fragments from the alpha and beta chains of the fibrinogen molecule and creates fibrin monomers which subsequently become highly ordered as a polymerized fibrin clot. Moreover, thrombin acts as a potent physiologic stimulant to activate platelets (5-8). Platelets convert prothrombin into thrombin in the presence of calcium ion. Meanwhile, the amount of thrombin is raised and thus the severity of the reactions is inevitable (9). The end point of these reactions is the formation of fibrin polymer which still has a little consistency, but the electrostatic interactions between adjacent fibrin monomer molecules will strengthen it (10, 11). The final blood clotting stability is achieved by activating factor XIII, or the same fibrin stabilizing factor which involves the

Table 1: Classification of Plants Based on Their Antiplatelet Property.

Row	Scientific Name	Family	Discovered Anti-Platelet Aggregation Effect
1	Urtica dioica	Urticaceae	Urtica dioica extract produced a dose-dependent inhibition of thrombin and ADP-induced aggregation. The plant might be efficient due to its polyphenolic compounds present in their extracts that is indicative of their involvement in the treatment or prevention of platelet aggregation complications associated with cardiovascular diseases (32).
2	Angelica genuflexa	Apiaceae	Five coumarins were isolated from the MeOH extract of Angelica genuflexa in the course of searching for anti-platelet and anti-coagulant components from the plant. Pabulenol and osthol were observed to be either equally effective or 2-4 times more inhibitory than ASA in both arachidonic acid and U46619 (TXA2 mimetic) induced platelet aggregations (33).
3	Artemisia capillaris Thunb.	Asteraceae	Several constituents from A. capillaris possessed anti-platelet activity. Artemicapin B, capillarisin , quercetin , capillaridin A, capillaridin B, isoscopoletin, scopoletin, aesculetin and caffeic acid were capable of inhibiting the platelet aggregation mediated by AA and collagen. Capillaridin C, capillene, capillin and O-methoxycapillene inhibited platelet aggregation induced by AA, collagen, PAF and thrombin. Arcapillin showed inhibitory effect at low concentration but caused spontaneous platelet aggregation at high concentrations without inducer (42).
4	Cinchona officinalis L.	Rubiaceae	Cinchonine from the cinchona bark demonstrated inhibitory effect on platelet aggregation induced by epinephrine, ADP, PAF, collagen and Ca 2+ ionophore, A-23187 in a concentration dependent manner. Inhibition of protein kinase C activator and phorbol myristate acetate together with low doses of PAF (80 nM) was also observed. The anti-platelet effect observed was found to be mainly mediated through the inhibition of Ca 2+ influx and protein kinase C pathways in human platelets (43).
5	Ginkgo biloba L.	Ginkgoaceae	G. biloba extract proved to be capable of inhibiting platelet aggregation by increasing the concentrations of endothelium-derived thrombolytics. Ginkgolide B, isolated from the terpene fraction of the extract demonstrated inhibitory effect on PAF (44).
6	Camellia sinensis	Theaceae	Green tea catechins exhibited inhibitory effect on collagen, AA and U46619 induced rabbit platelet aggregation in vitro in a concentration-dependent way. When administered to rats, the catechins inhibited AA induced platelet aggregation ex vivo. Catechins also inhibited thromboxane A2 and Prostaglandin D2 synthesis induced by AA in intact rabbit platelets as well as ATP release from dense granules in washed platelets (45).

creation of a covalent bond between the lysine amino acids with glutamine in the chain between the alpha and the adjacent Y in fibrin molecules (12-14). Factor XIII can bind a physiological fibrinolysis inhibitor to a fibrin clot with covalent bonding. As a result, the corresponding clot will be less sensitive to the lysis of the plasmin. If platelet exists during the formation of the clot, the resulting clot is totally constricted and contracted due to the contraction of a platelet protein (15, 16).

The blood coagulation process is one of the most important and vital physiological processes in the human body which is affected by many factors and many congenital and acquired defects, and each of these factors can affect the coagulation process and cause many problems for humans (17-19).

The most important disorders associated with the blood coagulation system are diseases like Hemophilia A, B and C, Von Willebrand disease, Bernard-Soulier syndrome, Glanzmann thrombasthenia , etc. (20-23).So far, many medicinal plants have been discovered that have various properties on the human coagulation system (24, 25). Since ancient times, some plants have been used, even topically, to stop the bleeding of the wound. Furthermore, other herbs which are still in use and often have dramatic effects,

Table 2: Classification of Plants Based on Their Anticoagulant Activity.

Row	Scientific Name	Family	Discovered Anti-Blood Coagulation Effect
1	Ferula communis	Apiaceae	The prenylated coumarin ferulenol that was obtained from this plant did not have a direct impact on blood coagulation. However, it exhibited hepatocyte cytotoxicity and hindered factor X biosynthesis (40% reduction) at non-cytotoxic concentrations (<100 nM). Studies that have evaluated ferulenol derivatives have indicated the prenyl residue as the main determinant of ferulenol activity (36).
2	Glycyrrhiza glabra	Fabaceae	Intravenous administration of GL resulted in a dose-dependent decrease in the level of thrombus on a venous thrombosis model that combines stasis and hypercoagulability. GL doses of 180 mg/kg body weight reduced 93% of thrombus weight. This impact indicated a time-dependent pattern being remarkably decreased when the thrombogenic stimulus was applied 60 min after drug administration. Moreover, GL could prevent thrombosis via an arteriovenous shunt model. GL doses of 180 and 360 mg/kg reduced the thrombus weight by 35 and 90%, respectively. Accordingly, the APTT ex vivo was enhanced by 1.5- and 4.3-fold at GL doses of 180 and 360 mg/kg, respectively. Furthermore, GL doses above 90 mg/kg brought about noticeable hemorrhagic effect. Unlike heparin, GL was not able to potentiate the inhibitory activity of antithrombin III or heparin cofactor II towards thrombin. On the whole, data shows that GL is an efficient thrombin inhibitor in vivo, which might be indicative of its other known pharmacological properties (38).
3	Artemisia herba	Asteraceae	An anti-coagulant component was isolated from Artemisia herba by DEAE-cellulose, Sephadex G-75 and Sephadex LH-20 column chromatography. This acidic polysaccharide has an average molecular weight of 10,000 and is composed of galacturonic acid and rhamnose (46).
4	Melilotus officinalis	Fabaceae	The first plant derived coumarin anti-coagulant discovered was dicoumarol, 3,3'-methylenebis-4- hydroxycoumarin isolated from spoiled sweet clover hay. It caused a lethal haemorrhagic disease of cattle due to its anti-coagulant effect. A famous 4-hydroxycoumarin synthesized based on the backbone structure of dicoumarol is warfarin (47).
5	Bauhinia forticata L.	Fabaceae	Aqueous extract from aerial parts of Bauhinia forficate demonstrated anti-coagulant activity against clotting activity induced by Bothrops and Crotalus crude venoms, indicating the presence of a highly active component (48).

are used either orally to strengthen the body's coagulation system or as a source of vitamin K (26, 27). Besides, some herbs are used by people who have high blood concentration level for the purpose of the dilution of their blood and prevention of diseases and problems (28, 29). Among the most important properties of medicinal plants is the lack of or low level of side effects and drug interactions while human-made chemicals often have highly serious side effects (30).

The aim of this study was to investigate the properties of some of the most effective medicinal plants affecting the blood coagulation process in order to provide a suitable basis for future studies. It can also be considered as a source for further study of this topic to introduce new ideas for the utilization of these plants in the production of effective and low cost drugs.

Methodology

Related articles were searched from Google Scholar, PubMed, ScienceDirect, HighWire, MD Consult and Scopus data bases.

Forty-six articles were chosen for this research, but after primary screening 14 articles were eliminated due to duplication and irrelevant content. Finally, after another revision, 19 articles were included in the

Table 3: Plants with Antiplatelet and Anticoagulant Activity.

Row	Scientific Name	Family	Discovered Anti-Platelet Aggregation Effect	Discovered Anti-Blood Coagulation Effect
1	Erigeron canadensis	Asteraceae	The polyphenolic-polysaccharide preparation from Erigeron canadensis L. was isolated by multi-step process. The whole preparation had anti-platelet activity, limited to the cyclooxygenase pathway, induced by arachidonic acid (31).	The polyphenolic-polysaccharide obtained from Erigeron canadensis L. was isolated via multi-step process. The preparation exhibited in vivo anticoagulant property. Preparations had an inhibitory effect on thrombin as well as factor Xa amidolytic activities in the presence of antithrombin. However, much higher concentrations were required to obtain the same effects like that of unfractionated heparin. The mechanisms of anticoagulant property in the case of the plant preparation are based on interactions with heparin cofactor II, to inactivate thrombin (31).
2	Paeonia lactiflora and Paeonia suffruticosa	Paeoniaceae (both)	Eighteen compounds, which have been indicated in previous studies to exist in both plant medicines, were investigated for their impacts on platelet aggregation and blood coagulation. Paeonol (5), paeoniflorin (9), benzoyl paeoniflorin (11), and benzoyloxy paeoniflorin (12) were found to be the main active constituents. They would collectively have significant impact on the improvement of blood circulation through their inhibitory effects on both platelet aggregation and blood coagulation. Moreover, methylgallate (4), (+)-catechin (7), paeoniflorigenone (8), galloylpaeoniflorin (13), and daucosterol (16) might also be effective in improving blood circulation by hindering either platelet aggregation and/or blood coagulation (34).	Eighteen compounds, which have been shown to exist in both plant medicines, had anti-coagulant activity (34).
3	Rheum undulatum	Polygonaceae	Three known stilbenes (desoxyrhapontigenin, rhapontigenin, and piceatannol) have been examined for their effects on blood platelet aggregation. Both rhapontigenin and desoxyrhapontigenin demonstrated significant inhibitory effects on the aggregation caused by arachidonic acid and collagen (35).	Piceatannol, obtained from the plant, did not have any inhibitory effect. These inhibitory effects might contribute to some extent to anti-blood stagnancy activity of rhubarb (35).
4	Cinnamomum cassia	Lauraceae	An extract of this plant was found to have both platelet anti-aggregation and blood anti-coagulation impacts in preliminary testing. Among the 13 compounds extracted from this plant, eugenol (2), amygdalactone (4), cinnamic alcohol (5), 2-hydroxycinnamaldehyde (7), 2-methoxycinnamaldehyde (8), and	An extract of this plant exhibited both platelet anti-aggregation and blood anti-coagulation impacts in preliminary testing. Bevertheless, the 13 compounds were only patially effective against blood coagulation (37).

coniferaldehyde (9) demonstrated 1.5–73-fold greater inhibitory impacts than acetylsalicylic acid (ASA) on arachidonic acid (AA)-induced aggregation (50% inhibitory concentration [IC50] = 3.8, 5.16, 31.2, 40.0, 16.9, and 0.82 μM, respectively, vs. 60.3 μM) and 6.3–730-fold stronger effect than ASA on U46619 (a thromboxane A2 mimic)-induced aggregation (IC50 = 3.51, 33.9, 31.0, 51.3, 14.6, and 0.44 μM, respectively, vs. 321 μM). The other compounds, coumarin (3), cinnamaldehyde (6), cinnamic acid (10), icariside DC (11), and dihydrocinnacasside (12), also inhibited (2.5 to four times greater than ASA) U46619-induced aggregation. In addition, compounds 2, 4, 5, 6, 7, 8, and 9 were 1.3–87 times more effective than ASA against epinephrine-induced aggregation (IC50 = 1.86, 1.10, 37.7, 25.0, 16.8, 15.3, and 0.57 μM, respectively, vs. 50.0 μM).

All in all, compounds 2, 4, 8, and 9 exhibited greater inhibitory properties than others on AA-, U46619-, and epinephrine-induced platelet aggregation.

Eugenol (2) and coniferaldehyde (9) were the two of the most active anti-platelet constituents of C. cassia (37).

5	Allium sativum L.	Amaryllidaceae	Methyl allyl trisulfide extracted from garlic inhibited platelet aggregation caused by AA (39).	Methyl allyl trisulfide extracted from garlic hindered the production of thromboxane B2, 12-hydroxyhepta-decatrienoic acid, prostaglandin E2 and 12-hydroxyeicosatetraenoic acid (39).
6	Acacia nilotica L.	Acacia nilotica L.	The extract of A. nilotica inhibited platelet aggregation induced by arachidonic acid (AA) (40).	The extract of A. nilotica inhibited adenosine diphosphate (ADP), platelet activating factor (PAF), Ca 2+ ionophore A- 23187 and collagen in a concentration dependent manner (40).
7	Angelica pubescens Maxim	Apiaceae	As an active component of A. pubescens, Osthole could inhibit platelet aggregation (41).	Osthole extracted from this plant demonstrated inhibition of ATP release by preventing thromboxane generation and phosphoinositides breakdown (41).
8	Eleutherococcus senticosus	Araliaceae	Eleutherococcus senticosus contains a constituent that inhibits platelet aggregation.	Ninety white adult Wistar rats and 20 healthy young (18-23 years) people were examined with regard to the state of plasma. The purpose of the study was evaluate the effect of Eleutherococcus on the parameters of coagulant, anticoagulant and fibrinolytic blood plasma systems in unadapted organism. According to the research, a 30-day administration of adaptogen raises the levels of antithrombin III in rat plasma and plasma anticoagulant reserves of unadapted animals and people. The results confirm a specific activity of Eleutherococcus extract which optimizes the anticoagulant properties

of blood. Consequently, the course administration of adaptogen improves adaptation concerning the impact of stress factors, shifting hemostatic potential in the direction of blood hypercoagulability. The keywords of this study included adaptogen, Eleutherococcus, hemostasis, stress, anticoagulant activity (49).

study.

Anti-Coagulant Properties of the Surveyed Medicinal Plants

Twenty medicinal plants were found to have effective active ingredients for inhibiting platelet aggregation and blood coagulation.

These plants are Erigeron Canadensis, Urtica dioica, Angelica genuflexa, Paeonia lactiflora, Paeonia suffruticosa, Rheum undulatum, Ferula communis, Cinnamomum cassia, Glycyrrhiza glabra, Allium sativum L., Acacia nilotica L., Angelica pubescens Maxim, Artemisia capillaris Thunb., Cinchona officinalis L., Ginkgo biloba L., Ginkgo biloba L., Camellia sinensis, Artemisia herba, Melilotus officinalis, Bauhinia forticata L., and Eleutherococcus senticosus.

Discussion and Conclusion

One of the major goals of this study was to create a scientific and appropriate literature review of effective medicinal herbs with anticoagulation effects. In this study, 20 medicinal herbs were selected and examined. One of the conclusions that can be drawn from this study is that many of the plants with anti-coagulant activity belong to the Fabaceae family. Furthermore, common members of other plant families were included in this study which expresses and confirms that they have common properties in the members of a plant family even though they are completely different.

One of the most important problems in our study was the impossibility of comparing the anticoagulant power of each plant with other plants surveyed in this research. One of the reasons for this was the existence of different test and measurement systems many of which were not standardized in the articles. Moreover, this study was limited to a small number of plants. There might be other plants efficient in preventing blood coagulation not included in this research.

Finally, this study indicated that there are many medicinal herbs that have different effective substances to prevent blood coagulation by various mechanisms. These plants can be considered as highly significant and efficient resources for producing valuable drugs against diseases that are caused by blood coagulation. Some of these plants naturally grow in nature and the rest are easily nurtured. Hence, medicinal herbs can be converted into drugs which, despite having complex and valuable materials, have a very low production cost and other benefits including low side effects.

Conflict of Interest

The authors declare that they have no conflict of interest.

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