

## Review Article

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

Hossein Elyasi<sup>1</sup>, Hadis Rahimi<sup>1</sup>, Ali Asghar Kiani<sup>2, 3\*</sup>

<sup>1</sup>Student Research Committee, Faculty of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

<sup>2</sup>Department of Hematology and Blood Banking, Lorestan University of Medical Sciences, Khorramabad, Iran

<sup>3</sup>Razi Herbal Medicines Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran.

Received: 25.01.2018; Accepted: 10.03.2018

## 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

**\*Corresponding Author:** Ali Asghar Kiani, Department of Hematology and Blood Banking, Lorestan University of Medical Sciences, Khorramabad, Iran. Email: aliasgharkiani@gmail.com.

**Please cite this article as:** Kiani A A, Elyasi H, Rahimi H. A Review of Medicinal Herbs Capable of Preventing Blood Coagulation and Platelet Aggregation. *Herb. Med. J.* 2017;2(4):in press.

## 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

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

Row	Scientific Name	Family	Discovered Anti-Platelet Aggregation Effect
1	<i>Urtica dioica</i>	Urticaceae	<i>Urtica dioica</i> 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	<i>Angelica genuflexa</i>	Apiaceae	Five coumarins were isolated from the MeOH extract of <i>Angelica genuflexa</i> 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	<i>Artemisia capillaris</i> Thunb.	Asteraceae	Several constituents from <i>A. capillaris</i> 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	<i>Cinchona officinalis</i> L.	Rubiaceae	Cinchonine from the cinchona bark demonstrated inhibitory effect on platelet aggregation induced by epinephrine, ADP, PAF, collagen and Ca <sup>2+</sup> 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 <sup>2+</sup> influx and protein kinase C pathways in human platelets (43).
5	<i>Ginkgo biloba</i> L.	Ginkgoaceae	<i>G. biloba</i> 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	<i>Camellia sinensis</i>	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 A <sub>2</sub> and Prostaglandin D <sub>2</sub> synthesis induced by AA in intact rabbit platelets as well as ATP release from dense granules in washed platelets (45).

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 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

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

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).

Row	Scientific Name	Family	Discovered Anti-Blood Coagulation Effect
1	<i>Ferula communis</i>	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	<i>Glycyrrhiza glabra</i>	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	<i>Artemisia herba</i>	Asteraceae	An anti-coagulant component was isolated from <i>Artemisia herba</i> 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	<i>Melilotus officinalis</i>	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	<i>Bauhinia forficata</i> L.	Fabaceae	Aqueous extract from aerial parts of <i>Bauhinia forficata</i> demonstrated anti-coagulant activity against clotting activity induced by Bothrops and Crotalus crude venoms, indicating the presence of a highly active component (48).

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, 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,

**Table 3:** Plants with Antiplatelet and Anticoagulant Activity.

Row	Scientific Name	Family	Discovered Anti-Platelet Aggregation Effect	Discovered Anti-Blood Coagulation Effect
1	<i>Erigeron canadensis</i>	Asteraceae	The polyphenolic-polysaccharide preparation from <i>Erigeron canadensis</i> 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 <i>Erigeron canadensis</i> 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	<i>Paeonia lactiflora</i> and <i>Paeonia suffruticosa</i>	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	<i>Rheum undulatum</i>	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	<i>Cinnamomum cassia</i>	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 coniferaldehyde (9) demonstrated	An extract of this plant exhibited both platelet anti-aggregation and blood anti-coagulation impacts in preliminary testing. Nevertheless, the 13 compounds were only partially effective against blood coagulation (37).

			<p>1.5–73-fold greater inhibitory impacts than acetylsalicylic acid (ASA) on arachidonic acid (AA)-induced aggregation (50% inhibitory concentration [IC<sub>50</sub>] = 3.8, 5.16, 31.2, 40.0, 16.9, and 0.82 <math>\mu</math>M, respectively, vs. 60.3 <math>\mu</math>M) and 6.3–730-fold stronger effect than ASA on U46619 (a thromboxane A<sub>2</sub> mimic)-induced aggregation (IC<sub>50</sub> = 3.51, 33.9, 31.0, 51.3, 14.6, and 0.44 <math>\mu</math>M, respectively, vs. 321 <math>\mu</math>M). The other compounds, coumarin (3), cinnamaldehyde (6), cinnamic acid (10), icaraside 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 (IC<sub>50</sub> = 1.86, 1.10, 37.7, 25.0, 16.8, 15.3, and 0.57 <math>\mu</math>M, respectively, vs. 50.0 <math>\mu</math>M). 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 <i>C. cassia</i> (37).</p>	
5	<i>Allium sativum</i> 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 B <sub>2</sub> , 12-hydroxyheptadecatrienoic acid, prostaglandin E <sub>2</sub> and 12-hydroxyicosatetraenoic acid (39).
6	<i>Acacia nilotica</i> L.	<i>Acacia nilotica</i> L.	The extract of <i>A. nilotica</i> inhibited platelet aggregation induced by arachidonic acid (AA) (40).	The extract of <i>A. nilotica</i> inhibited adenosine diphosphate (ADP), platelet activating factor (PAF), Ca <sup>2+</sup> ionophore A-23187 and collagen in a concentration dependent manner (40).
7	<i>Angelica pubescens</i> Maxim	Apiaceae	As an active component of <i>A. pubescens</i> , 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	<i>Eleutherococcus senticosus</i>	Araliaceae	<i>Eleutherococcus senticosus</i> 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 <i>Eleutherococcus</i> 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 <i>Eleutherococcus</i> 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).

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 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.

## References

1. Ryu JK, Petersen MA, Murray SG, Baeten KM, Meyer-Franke A, Chan JP, Vagena E, Bedard C, Machado MR, Coronado PE, Prod'homme T. Blood coagulation protein fibrinogen promotes autoimmunity and demyelination via chemokine release and antigen presentation. *Nature communications*. 2015;6:8164.
2. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood reviews*. 2015;29(1):17-24.
3. Park CY, Kim J, Kweon J, Son JS, Lee JS, Yoo JE, Cho SR, Kim JH, Kim JS, Kim DW. Targeted inversion and reversion of the blood coagulation factor 8 gene in human iPS cells using TALENs. *Proceedings of the National Academy of Sciences*. 2014;111(25):9253-8.
4. Koshlar RL, Somajo S, Norström E, Dahlbäck B. Erythrocyte-derived microparticles supporting activated protein C-mediated regulation of blood coagulation. *PLoS One*. 2014;9(8):e104200.
5. Hethershaw EL, Cilia La Corte AL, Duval C, Ali M, Grant PJ, Ariens RA, Philippou H. The effect of blood coagulation factor XIII on fibrin clot structure and fibrinolysis. *Journal of Thrombosis and Haemostasis*. 2014;12(2):197-205.
6. Butenas S, Mann KG. The effect of corn trypsin inhibitor and inhibiting antibodies for FXIa and FXIIa on coagulation of plasma and whole blood: comment. *Journal of Thrombosis and*

- Haemostasis. 2015;13(3):487-8.
7. Wannamethee SG, Whincup PH, Papacosta O, Lennon L, Lowe GD. Associations between blood coagulation markers, NT-proBNP and risk of incident heart failure in older men: The British Regional Heart Study. *International journal of cardiology*. 2017;230:567-71.
  8. Sakimoto S, Hagio T, Yonetomi Y, Ono T, Koyama S, Hashimoto A, Gohda M, Sakai M, Nishiyama T, Tanaka K, Matsuya H. Abstract WP286: ONO-8610539, an Injectable Small-Molecule Inhibitor of Blood Coagulation Factor XIa, Improves Cerebral Ischemic Injuries Associated with Photothrombotic Occlusion of Rabbit Middle Cerebral Artery.
  9. Maitz MF, Zitzmann J, Hanke J, Renneberg C, Tsurkan MV, Sperling C, Freudenberg U, Werner C. Adaptive release of heparin from anticoagulant hydrogels triggered by different blood coagulation factors. *Biomaterials*. 2017;135:53-61.
  10. Dasgupta SK, Thiagarajan P. MFG-E8 in the Blood Cell Homeostasis and Coagulation. In *MFG-E8 and Inflammation 2014* (pp. 65-84). Springer Netherlands.
  11. Nie S, Tang M, Yin Z, Wang L, Sun S, Zhao C. Biologically inspired membrane design with a heparin-like interface: prolonged blood coagulation, inhibited complement activation, and bio-artificial liver related cell proliferation. *Biomaterials Science*. 2014;2(1):98-109.
  12. Ebert J, Wilgenbus P, Horke S. Paraoxonase-2 Regulates Blood Coagulation through Endothelial Redox-Signaling and Inflammation.
  13. Han L, Liu X, Li H, Zou J, Yang Z, Han J, Huang W, Yu L, Zheng Y, Li L. Blood coagulation parameters and platelet indices: changes in normal and preeclamptic pregnancies and predictive values for preeclampsia. *PloS one*. 2014 Dec 2;9(12):e114488.
  14. Kushida T, Saha K, Subramani C, Nandwana V, Rotello VM. Effect of nano-scale curvature on the intrinsic blood coagulation system. *Nanoscale*. 2014;6(23):14484-7.
  15. Tomkiewicz-Pajak L, Hoffman P, Trojnarowska O, Lipczyńska M, Podolec P, Undas A. Abnormalities in blood coagulation, fibrinolysis, and platelet activation in adult patients after the Fontan procedure. *The Journal of thoracic and cardiovascular surgery*. 2014;147(4):1284-90.
  16. Altemose B, Robson MG, Kipen HM, Strickland PO, Meng Q, Gong J, Huang W, Wang G, Rich DQ, Zhu T, Zhang J. Association of air pollution sources and aldehydes with biomarkers of blood coagulation, pulmonary inflammation, and systemic oxidative stress. *Journal of Exposure Science and Environmental Epidemiology*. 2017;27(3):244.
  17. Khan S, Davenport R, Raza I, Glasgow S, De'Ath HD, Johansson PI, Curry N, Stanworth S, Gaarder C, Brohi K. Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma hemorrhage. *Intensive care medicine*. 2015;41(2):239-47.
  18. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer EA. The European guideline on management of major bleeding and coagulopathy following trauma. *Critical care*. 2016;20(1):100.
  19. Massicotte L, Thibeault L, Roy A. Classical notions of coagulation revisited in relation with blood losses, transfusion rate for 700 consecutive liver transplantations. In *Seimens in thrombosis and hemostasis*. Thieme Medical Publishers. 2015;41(5):548-46.
  20. Tenorio AR, Zheng Y, Bosch RJ, Krishnan S, Rodriguez B, Hunt PW, et al. Soluble markers of inflammation and coagulation but not T-cell activation predict non-AIDS-defining morbid events during suppressive antiretroviral treatment. *The Journal of infectious diseases*. 2014;210(8):1248-59.
  21. Hajat A, Allison M, Diez-Roux AV, Jenny NS, Jorgensen NW, Szpiro AA, Vedral S, Kaufman JD. Long-term exposure to air pollution and markers of inflammation, coagulation, and endothelial activation: a repeat-measures analysis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Epidemiology* (Cambridge, Mass.). 2015;26(3):310.
  22. Bu F, Maga T, Meyer NC, Wang K, Thomas CP, Nester CM, Smith RJ. Comprehensive genetic analysis of complement and coagulation genes in atypical hemolytic uremic syndrome. *Journal of the American Society of Nephrology*. 2014;25(1):55-64.
  23. Dogan MV, Shields B, Cutrona C, Gao L, Gibbons FX, Simons R, et al. The effect of smoking on DNA methylation of peripheral blood mononuclear cells from African American women. *BMC genomics*. 2014;15(1):151.
  24. Tomlinson TR, Akerele O, editors. *Medicinal plants: their role in health and biodiversity*. University of Pennsylvania press; 2015 Jun 30.
  25. Bahmani M, Zargaran A, Rafieian-Kopaei M, Saki K. Ethnobotanical study of medicinal plants used in the management of diabetes mellitus in the Urmia, Northwest Iran. *Asian Pacific journal of tropical medicine*. 2014;7:S348-54.
  26. Al-Snafi AE. Therapeutic properties of medicinal plants: a review of plants with hypolipidemic, hemostatic, fibrinolytic and anticoagulant effects (part I). *Asian Journal of Pharmaceutical Science & Technology*. 2015;5(4):271-84.
  27. Asad B, Hassan MH, Choudary BA, Asad AF, Muratza G, Hussain I. Compensatory effects of medicinal plants of Pakistan upon prolongation of coagulation assays induced by Naja naja karachiensis bite. *Current Science* (00113891). 2014;106(6).
  28. Rouhi-Boroujeni H, Heidarian E, Rouhi-Boroujeni H, Deris F, Rafieian-Kopaei M. Medicinal Plants with multiple effects on cardiovascular diseases: a systematic review. *Current pharmaceutical design*. 2017;23(7):999-1015.
  29. Pour MA, Sardari S, Eslamifard A, Rezvani M, Azhar A, Nazari M. Evaluating the anticoagulant effect of medicinal plants in vitro by cheminformatics methods. *Journal of herbal medicine*. 2016;6(3):128-36.
  30. Iwu MM. *Handbook of African medicinal plants*. CRC press; 2014 Feb 4.
  31. Pawlaczyk I, Czerchawski L, Kuliczowski W, Karolko B, Pilecki W, Witkiewicz W, Gancarz R. Anticoagulant and anti-platelet activity of polyphenolic-polysaccharide preparation isolated from the medicinal plant *Erigeron canadensis* L. *Thrombosis Research*. 2011;127(4):328-40.
  32. Mekhfi H, El Haouari M, Legssyer A, Bnouham M, Aziz M, Atmani F, Remmal A, Ziyat A. Platelet anti-aggregant property of some Moroccan medicinal plants. *Journal of ethnopharmacology*. 2004 Oct 31;94(2):317-22.
  33. Lee YY, Lee S, Jin JL, Yun-Choi HS. Platelet anti-aggregatory effects of coumarins from the roots of *Angelica genuflexa* and *A. gigas*. *Archives of pharmacological research*. 2003;26(9):723-6.
  34. Koo YK, Kim JM, Koo JY, Kang SS, Bae K, Kim YS, et al. Platelet anti-aggregatory and blood anti-coagulant effects of compounds isolated from *Paeonia lactiflora* and *Paeonia suffruticosa*. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*. 2010;65(8):624-8.
  35. Ko SK, Lee SM, Whang WK. Anti-platelet aggregation activity of stilbene derivatives from *Rheum undulatum*. *Archives of pharmacological research*. 1999;22(4):401-3.
  36. Monti M, Pinotti M, Appendino G, Dallochio F, Bellini T, Antognoni F, et al. Characterization of anti-coagulant properties of prenylated coumarin ferulenol. *Biochimica et Biophysica Acta (BBA)-General Subjects*. 2007;1770(10):1437-40.
  37. Kim SY, Koo YK, Koo JY, Ngoc TM, Kang SS, Bae K, et al. Platelet anti-aggregation activities of compounds from *Cinnamomum cassia*. *Journal of medicinal food*. 2010;13(5):1069-74.
  38. Mendes-Silva W, Assafim M, Ruta B, Monteiro RQ, Guimarães JA, Zingali RB. Antithrombotic effect of Glycyrrhizin, a plant-

- derived thrombin inhibitor. *Thrombosis research*. 2003;112(1):93-8.
39. Chan KC, Yin MC, Chao WJ. Effect of diallyl trisulfide-rich garlic oil on blood coagulation and plasma activity of anticoagulation factors in rats. *Food and chemical toxicology*. 2007;45(3):502-7.
40. Asad M, Aslam M, Munir TA, Nadeem A. Effect of *Acacia nilotica* leaves extract on hyperglycaemia, lipid profile and platelet aggregation in streptozotocin induced diabetic rats. *J Ayub Med Coll Abbottabad*. 2011;23(2):3-7.
41. Tiehong Y, Min J, Qibing M, Peng S. Effects of Angelica Polysaccharide on Blood Coagulation and Platelet Aggregation. *Journal of Chinese Medicinal Materials*. 2002;5:021.
42. Liu B, Wang SM, Wang BL, Xu YT, Yan EL, Hu XG, et al. Anticoagulant activity of cyclic dipeptides from *Sparganii Rhizoma*. *Chinese Traditional Patent Medicine*. 2015;1:007.
43. Carratù B, Federici E, Gallo FR, Geraci A, Guidotti M, Multari G, et al. Plants and parts of plants used in food supplements: an approach to their safety assessment. *Annali dell'Istituto superiore di sanita*. 2010;46(4):370-88.
44. Bone KM. Potential interaction of *Ginkgo biloba* leaf with antiplatelet or anticoagulant drugs: what is the evidence?. *Molecular nutrition & food research*. 2008;52(7):764-71.
45. Cai W, Xie L, Chen Y, Zhang H. Purification, characterization and anticoagulant activity of the polysaccharides from green tea. *Carbohydrate polymers*. 2013;92(2):1086-90.
46. Adam SE, Al-Qarawi AA, Elhag EA. Effects of various levels of dietary *Artemisia abyssinica* leaves on rats. *Laboratory animals*. 2000;34(3):307-12.
47. Yarnell E, Abascal K. Plant coumarins: Myths and realities. *Alternative and Complementary Therapies*. 2009;15(1):24-30.
48. Oliveira CZ, Maiorano VA, Marcussi S, Sant'Ana CD, Januário AH, Lourenço MV, et al. Anticoagulant and antifibrinolytic properties of the aqueous extract from *Bauhinia forficata* against snake venoms. *Journal of Ethnopharmacology*. 2005;98(1):213-6.
49. Oates L. Siberian ginseng: *Eleutherococcus senticosus*. *Journal of Complementary Medicine: CM, The*. 2008;7(4):44.