Review Article

Anti-coagulant Activity of Flavonoids in Medicinal Plants from Philippine Flora: A Narrative Review

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ABSTRACT

Anti-coagulants are essential in preventing the formation of clots which otherwise can lead to strokes and heart attacks if not given to people with a high risk of getting clots. Several medicinal plants that can be found in the Philippines have anti-coagulant properties and this can be attributed to the bioactive substance, flavonoids. A critical analysis of the journals, coming from Google Scholar, ScienceDirect, and PubMed, that was related to the study was conducted. We found 10 different medicinal plants from the Philippines that contain flavonoids and have an anti-coagulant mechanism. Almost all the plants showed inhibition of thrombin and factor X. It was also reported that different flavonoids such as flavonols, quercetin, rutin, kaempferol, etc. are responsible for these mechanisms. The results show that medicinal plants from the Philippines particularly those containing flavonoids have the capacity to prevent coagulation and can be a potential source of treatment.

Key words: Anti-coagulant, Clot inhibitor, Flavonoids, Philippine medicinal plants, aPTT, prothrombin time.

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INTRODUCTION

SARS-CoV-2, the virus associated with Coronavirus disease 2019 (COVID-19), primarily affects the respiratory system causing severe symptoms such as difficulty in breathing and chest pain. It is also not uncommon that this virus attacks other body system and cause a mild to life-threatening symptoms.[1] In a systematic review and meta-analysis done by Malas *et al.* in 2020, they found out that patients infected with Sars-CoV-2 could experience blood clots or hypercoagulability.[2] The outcome of this review involving 42 studies shows that out of 8271 patients, 21% have venous thromboembolism, 20% have deep vein thrombosis, 13% have a pulmonary embolism, and 2% have arterial thromboembolism. The percentage of these thromboembolism events among ICU patients is slightly higher. These events account for a 74% risk of mortality. With this significant rate of death, emerging experiments for potential treatment particularly flavonoids arise.

With their insufficiency of systemic toxicity, their established capacity to synergize with different conventional drugs, and with their functional groups that can communicate with various cellular targets and obstruct different pathways, flavonoids can be considered a prospective candidate to impede the lifecycle of the coronavirus.[3,4] In fact, recent studies hypothesized that these natural substances could inhibit two host serine-proteases, namely, TMPRSS2 and Furin, that can cleave the spike protein of SARS-CoV-2 that facilitates the virus' infectivity.[5,6] Also, it was found out that through inhibition of the enzymes papain-like protease, as well as 3-chymotrypsin-like protease, numerous flavonoids have antiviral effects antagonistic toward SARS- and MERS-CoV.[7]

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Medicinal plants have been utilized throughout the human history for treating various diseases. Their use becomes so significant in maintaining and supporting life all over the world, especially to those who lived in developing countries. According to the World Health Organization, about 80% of the world's population utilize medicinal plants for their primary health care needs.[8] In addition, out of all Food and Drug Administration (FDA)-approved drugs, more than one third (39.1%) are of natural origin, and roughly almost half (48.6%) of all the cancer drugs that were put on record from 1940s until the present times are either from natural products or their byproducts.[9] Through time, it was then proved that these natural products indeed have different active phytochemicals responsible for their therapeutic property, such as curcumins, alkaloids, flavonoids, plant sterols, and ligands to name a few.

In the Philippines, one of the archipelagic countries in Southeast Asia, herbal plant species are abundant. As it became a custom by the Filipinos, these herbal plants are utilized as an alternative and first aid medicines to ease minor illnesses, such as coughs, colds, flu, cuts, and other infections. In fact, besides the implementation of Republic Act No. 8423, also known as the "Traditional and Alternative Medicine Act (TAMA) of 1997", the Department of Health (DOH) of the Philippines also issued a list of "ten scientifically validated" medicinal plants in the Philippines in 1992, namely, *akapulco (Cassia alata), ampalaya (Momordica charantia), Allium sativium (bawang), bayabas (Psidium guajava), lagundi (Vitex negundo), niyug-niyogan (Quisqualis indica), sambong (Blumea balsamifera), tsaang-gubat (Ehretia microphylla), ulasimang bato (Peperomia pellucida),* and *yerba buena (Clinopodium douglassi)*.[10] Most of these plants also contain alkaloids, flavonoids, and tannins, as their bioactive metabolites, which give their potential to become a natural source of anti-coagulant.[9]

Anti-coagulants play an important role in hemostasis, a complex physiologic process that maintains the fluid state of the circulating blood and prevents abnormal bleeding when an injury occurs by producing a clot.[11] There are different active plant phytochemicals that have been determined, such as flavonoids, curcumins, flavonoids, plant sterols, alkaloids, and terpenoids, which give plants their anti-coagulant, as well as other pharmacological, properties. These phytochemicals have been utilized from the past through certain systems of traditional medicine to modern medicine, in which some of these become the source of certain conventional drugs.

Flavonoids, one of the naturally occurring phytochemicals found in plants, are a group of natural substances that are well known as an essential component in various pharmaceutical, nutraceutical, and medicinal applications. This is associated with their property being an anti-coagulant, anti-mutagenic, anti-inflammatory, and anti-carcinogenic, together with their ability to regulate the function of key cellular enzymes. They are also recognized as potent inhibitors for different enzymes, like cyclo-oxygenase (COX), xanthine oxidase (XO), and phosphoinositide 3-kinase, to name a few.[12] Although there are several factors, such as lipophilicity, poor solubility, and bioavailability, that hinder their potency and efficacy, it is still considered as a good source for the development and synthesis of new molecules for different therapeutic targets.[13]

Therefore, this review aims to present possible natural sources of anti-coagulant, particularly from the flavonoids of the different medicinal plants that can be found in the Philippines.

METHODOLOGY

Literature Search Strategy

A search of the electronic databases via PubMed and ScienceDirect, and electronic repositories via Google Scholar, was performed. The search was last performed in April 2021, using combinations of search terms, including "anti-coagulant" or "clot inhibitor" and "flavonoids" and "Philippines' medicinal plant". Except with the given exclusion criteria, literature search was done without any more limitations in order to find studies that focuses on how the medicinal plants in the Philippines can be an anti-coagulant.

Eligibility Criteria

Studies were included if, first, they showed anti-coagulant activities of medicinal plants found in the Philippines, second, they showed the presence of flavonoids as the primary chemical composition responsible for the anti-coagulant mechanism, third, they included clinical evidence of interaction of coagulation parameters, fourth, they had an assessment of the preclinical safety of the medicinal plants, and fifth, they had been published in the year 2011 to 2021. On the other hand, studies that were not written in English language, could not be assessed for free, written more than 10 years ago, and were published as a review or editorial were all excluded.

Selection Strategy

The eligibility of all potential studies that was identified for inclusion was initially assessed by all of the researchers, individually. Then, discrepancies regarding the study inclusions were resolved by two review-

ers, as well as through discussion with their adviser. The titles and abstracts were the first part of the journals that were verified, followed by the evaluation of the full texts. The list of the references of eligible articles or the relevant review papers were screened for the other eligible papers.

Data Extraction

The characteristics of eligible articles, such as the first author's last name, publication year, study design, subjects or participants, clinical evidence of interaction of coagulation parameters, as well as flavonoids responsible for anti-coagulant mechanism, and mechanism of action, were extracted by all six authors. The details of all the qualified articles are outlined in Table 1.

RESULTS

Our initial search retrieved 801 articles. After withdrawing duplicates, 713 titles and abstracts were screened. Out of all these articles, subsequently, 53 full texts were assessed for eligibility. Finally, 10 studies were included in this narrative review. A flowchart of the selection process is illustrated in Figure 1.

Anti-coagulant mechanism in plants with flavonoids

Flavonoids have shown to have an anti-coagulant property. Since they have inhibitory effects on platelets and white blood cells (WBCs), and have been demonstrated that they are capable of inhibiting platelet adhesion, aggregation, and secretion, they have become a potential interest in the development of natural

Table 1: Characteristics of the studies included.

Author	Study design; samples or participants	Plant	Clinical evidence of interaction of coagulation parameters
Kim *et al*. (2012)	Experimental study; Human plasma	*Curcuma longa*	• aPTT and PT were prolonged significantly at 5 uM concentration or greater
Ku *et al*. (2013)	Experimental study; Healthy volunteers in fasting status	*Oenanthe javanica*	• Prolonged aPTT and PT at concentrations greater than 2 um • Decreased fibrin polymerization rate
Bijak *et al*. (2011)	Experimental study; Healthy volunteers in fasting status	*Vitis vinifera*	• Prolonged aPTT and PT at concentrations of 5 and 50 ug/ml • Decreased fibrin polymerization rate
Ayodele *et al*. (2019)	Experimental study; healthy adult volunteers with no history of medication for at least one week	*Crossocephalum crepidiodes*	• aPTT and PT were both significantly increased at concentrations of the methanol extract and plant fractions
Edziri *et al*. (2019)	Experimental study; Healthy volunteers	*Beta vulgaris* L.	• aPTT and PT were significantly prolonged at 1 mg/mL methanol extract
Rehman *et al*. (2019)	Experimental study; Healthy white male albino rabbits	*Syzygium cumini*	• Bleeding time was significantly increased at 30th and 60th day • aPTT was significantly increased in both doses (i.e. 150 mg/kg and 500 mg/kg) • PT was increased at 60th day in 500 mg/kg dose
Félix-Silva *et al*. (2014)	Experimental study; Healthy adult volunteers in fasting status (at least 8 hr) and free from any medication for at least two weeks	*Jatropha gossypiifolia* L.	• Only aPTT was significantly prolonged
Rodrigues *et al*. (2015)	Experimental study; Human plasma	*Laguncularia racemosa*	• Thrombin time was significantly increased by hydroalcoholic and methanolic extracts
Pawlaczyk *et al*. (2011)	Experimental study; Standardized human plasma	*Erigeron canadensis* L.	• aPTT and PT were significantly prolonged
Khouya *et al*. (2015)	Experimental study; Healthy rats	*Thymus* spp.	• aPTT and PT were significantly prolonged

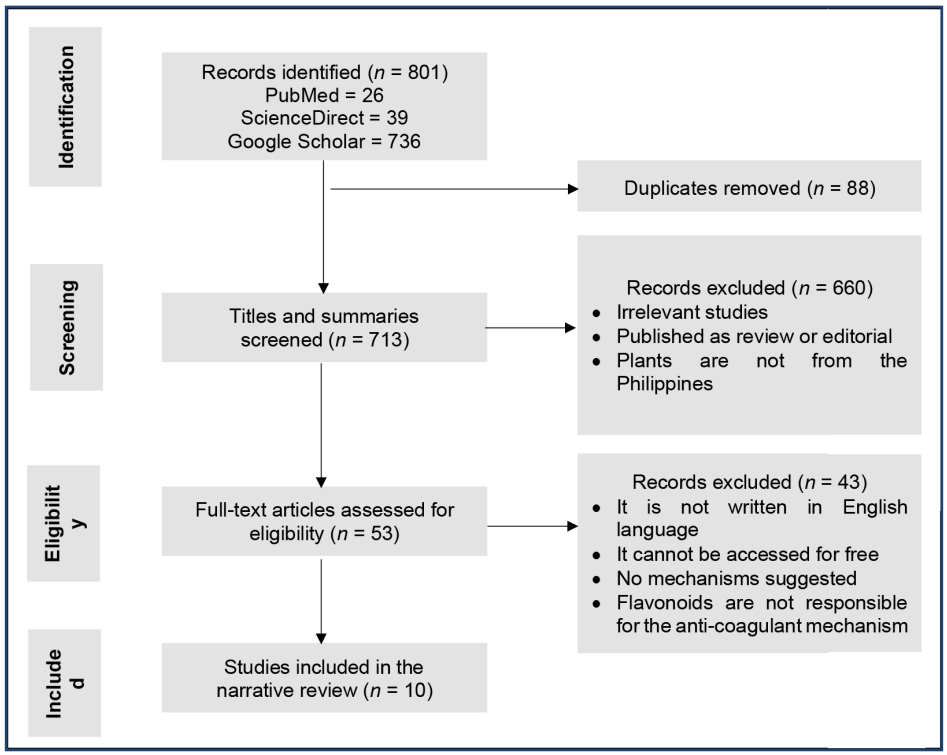

Figure 1: Flowchart of the study selection process.

and nontoxic blood inhibitors, as well as vessel wall interactions.[14] Table 2 shows that there are several mechanisms of actions possible, such as the inhibition of the intrinsic pathway, inhibition of the coagulation pathway, and inhibition of the common pathway, in which majority of the plants showed that they target thrombin and factor X*a*.

Thrombin inhibition

Thrombin is a key protease in the coagulation pathway. It cleaves fibrinopeptides to form fibrin, triggering clot formation and it also activates different factors such as factor V, VIII, and XI that amplifies coagulation mechanism and factor XIII which involved in stabilizing the clot. Therefore, if the thrombin is inhibited, fibrin generation and coagulation cascade will be ceased. Traditional anti-coagulant namely unfractionated heparin inhibits indirectly free thrombin while novel anti-coagulants focused more on finding direct inhibitors of thrombin.[15] Almost all the plants listed in Table 2 were reported to inhibit thrombin, and among them, flavonoids of *O.javanica,* namely persicarin and isorhamnetin, were reported to directly inhibit thrombin.[16]

Inhibition of factor Xa (FXa; activated Stuart-Prower factor)

The activated coagulation factor Xa (FXa), also known as the activated Stuart-Prower factor, is a serine protease actuated to take part in the coagulation process. It is part of the complex known as the prothrombinase, along with the activated factor V (FVa; activated labile factor) and prothrombin (factor II), which is essential in the activation of prothrombin from thrombin by cleaving Arg271 and Arg320.[17] In fact, it has been determined that one molecule of FXa can generate at least 1000 thrombin molecules, making it a novel target for modern anti-coagulant therapies. It is also currently being used as a medicine under the brand name ANDEXXA that reverses the influence of some anti-coagulation medications, which is needed when a patient has an out-of-control and life-threating bleeding. Table 2 shows that half of the listed plants found in the Philippines with anti-coagulant activity has factor Xa inhibition as their mechanism of action, namely, *O. javanica, C. longa, E. canadensis, T. vulgaris*, and *C. crepidioides*, with different responsible flavonoids. In a study conducted by Bijak *et al*., it was discovered that the flavonoids cyanidin and quercetin might be some of the prospective structural bases for designing direct inhibitors of FXa that are nontoxic, nature-based, and orally bioavailable.[18]

Inhibition of intrinsic coagulation pathway

The intrinsic coagulation pathway, measured by activated partial thromboplastin time (APTT), is activated through the contact initiation of factor XII (FXII),

Table 2: Plants found in the Philippines that has anti-coagulant mechanism through flavonoids.

Plants	Common Name(s)	Family	Flavonoids Responsible for Anti-coagulant Mechanism	Mechanism of Action	References
Oenanthe javanica	Water celery	Apiaceae	Persicarin and isorhamnetin	Directly inhibits FXa and amidolytic thrombin activity	[16]
Vitis vinifera	Grapes	Vitaceae	Flavanols	Inhibits amidolytic activity of thrombin	[18]
Curcuma longa	Turmeric	Zingiberaceae	Curcumin	Inhibits the generation of either thrombin or activated factor X (FXa)	[17]
Erigeron canadensis L.	Horseweed	Asteraceae	Quercetin, leutin, apigenin and flavones	Inhibits thrombin and factor Xa amidolytic activities in the presence of antithrombin.	[24]
Syzygium cumini	Java plum, black plum, duhat	Myrtaceae	Quercetin	Increases thrombin inhibition	[21]
Jatropha gossypiifolia L.	Tuba-tuba, bellyache bush	Euphorbiaceae	Isoorientin, orientin, and vitexin	Inhibits the intrinsic and/or common coagulation pathway	[22]
Crassocephalum crepidioides	Bulak Manok, redflower ragleaf, fireweed	Asteraceae	Catechin, rutin, and quercetin	Inhibits factors V, X and prothrombin of the common coagulation pathway	[19]
Beta vulgaris L.	Beet	Amaranthaceae	Myricetin, quercetin, rutin, and kampferol	Inhibits the intrinsic and/or common coagulation pathway	[20]
Laguncularia racemosa	White mangrove	Combretaceae	Quercetin-3-*O*-arabinoside (QAra) and quercetin-3-*O*-rhamnoside (Qn)	Inhibits thrombin	[23]
Thymus spp.	Thyme	Lamiaceae	Apigenin and luteolin	Inhibits extrinsic coagulation pathway, particularly factor VII, and factors V and X in common coagulation pathway	[25]

Legend: aPTT, activated partial thromboplastin time; PT, prothrombin time

followed by the activation of factors XI and IX. Then, this activated FIX (FIXa), along with its cofactor FVIIIa, form the intrinsic tenase complex, which plays an essential role in the coagulation cascade by converting factor X to Xa. Since this complex is the last rate-limiting step of the cascade involved in the intrinsic coagulation pathway, it is becomingly considered as an ideal target for the development of more secure anti-coagulants.[19] Among all the plants listed in Table 2, only *Jatropha gossypiifolia* L. and *Beta vulgaris* L. showed that their mechanism of action was the inhibition of intrinsic, as well as the common, coagulation pathway through their aqueous leaf and methanolic extract, respectively.[20,21]

Inhibition of extrinsic coagulation pathway

The extrinsic coagulation pathway, measured by prothrombin time, is known to be the shorter pathway of secondary homeostasis. When extrinsic pathway is already activated through a tissue factor (TF) released by endothelial cells after damage, TF goes on with the activation of factor VII to factor VIIa (FVIIa). Then, FVIIa activates factor X into factor Xa, which is known as start of the common pathway, where both the extrinsic and intrinsic pathways will linkup. Since FVIIa is the only known coagulation factor involved in the extrinsic pathway, prolonged prothrombin time is usually due to its lack of activity. Among all the plants listed in Table 2, only *Thymus* spp. shows that its mechanism of action involved was the inhibition of extrinsic coagulation pathway, in which their aqueous extracts had significantly increased PT, aPTT, and thrombin time (TT) dependent on their concentration. Thus, it was proven that the thyme species extracts significantly affects the principal coagulation pathways, namely intrinsic, extrinsic, and common.[22]

Inhibition of common coagulation pathway

The common coagulation pathway, measured by both prothrombin time (PT) and activated partial thromboplastin time (APTT), is stimulated by either the intrinsic or extrinsic pathways, resulting in the formation of blood clot. Factor X, produced by both pathways, signals the start of the common coagulation pathway, which leads to fibrin clot stabilization. The other factors involved include factors I, II, V, and VIII, which means targeting any of these factors results in

the interference of the common coagulation pathway. In Table 2, all of the plants listed inhibited common coagulation pathway, most of which particularly targets thrombin (FIIa) and FXa.

DISCUSSION

Flavonoids, a bioactive substance found in many plants, have a wide range of clinical use. Plants found in the Philippines that contain flavonoids are reportedly showing antioxidant, antibacterial, anti-inflammatory effects, etc. There are growing numbers of experimental studies about the anti-coagulant mechanism of flavonoids. It could indicate that flavonoids have the potential of preventing coagulation. As far as we are aware, this is the first review compiling plants found in the Philippines that contain flavonoids and assessing their anti-coagulant mechanism. It is hoped that presenting this review will provide the basis to consider the development of new drugs coming from plants containing flavonoids for preventing blood clots, especially those plants tested using human plasma; and the development of new studies testing the clinical effectiveness of plants tested against the rats to human plasma.

The mechanisms suggested have mostly involved inhibition of thrombin (factor IIa) and factor Xa (6 studies). In addition, suppression of the principal coagulation pathways, namely, the intrinsic, extrinsic, and common pathways were reported in 4 studies: three in the intrinsic and/or common pathways and one in the extrinsic and/or common pathways.

One of the strengths of this review include its use of an outcome classification for different possible mechanisms of plants and their flavonoids with regard to coagulation. It proves that the presence of flavonoid in the medicinal plants found in the Philippines can be used as a natural source of anti-coagulant. However, there are also limitations that must be taken into account. It should be indicated that all of the studies included only measured the anti-coagulant activity mechanisms *in vitro*. Moreover, the subjects of interest did not only focus on human participants as some journals used animals as test subjects. In spite of that, this review may encourage future researchers to further examine the subject. It may also give new information to health care professionals, as well as patients, about the potential utilization and also the risks associated with the misinformation in this matter.

Lastly, it is also important to take into account the possibility of biases across studies, including their publication, reporting and publishing bias, and performance, together with the prospective conflicts of interest; all of which could restrict our ability to produce potent and logical conclusions from these studies. Since we only had limited access to some journals, and studies that were not written in English language, could not be access without charge, and those that were published as review or editorial were excluded, it is most likely that a more comprehensive and thorough reporting of study results would enhance the quality of the evidence in further studies.

CONCLUSION AND RECOMMENDATIONS

In conclusion, there are different possible natural sources of anti-coagulant in the Philippines, particularly from the flavonoids of different medicinal plants. With their capacity to prevent coagulation through various anti-coagulant mechanisms, they can be a potential alternative source of a nontoxic, economical treatment. Further *in vivo* studies are needed to understand and elucidate comprehensively the anti-coagulant mechanism, as well as the prospective pharmacodynamic profile, of a particular plant and its flavonoids.

Authors' Contributions

All authors contributed to the data extraction and analysis, draft, and revision of the review. All of them gave final approval of the version to be passed and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Zhang Y, Geng X, Tan Y, Li Q, Xu C, Xu J, Hao L, Zeng Z, Luo X, Liu F, Wang H. New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. Biomed Pharmacother. 2020 Apr 28;127:110195. doi: 10.1016/j.biopha.2020.110195.
2. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. EClinicalmedicine. 2020 Dec 1;29:100639. doi: 10.1016/j.eclinm.2020.100639.
3. Russo M, Moccia S, Spagnuolo C, Tedesco I, Russo GL. Roles of flavonoids against coronavirus infection. Chem Biol Interact. 2020 Jul 28;328:109211. doi: 10.1016/j.cbi.2020.109211.
4. Spagnuolo C, Moccia S, Russo GL. Anti-inflammatory effects of flavonoids in neurodegenerative disorders. Eur J Med Chem. 2018 Jun 10;153:105-15. doi: 10.1016/j.ejmech.2017.09.001, PMID 28923363.
5. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020 Apr 16;181(2):271-280.e8. doi: 10.1016/j.cell.2020.02.052, PMID 32142651.
6. Rahman N, Basharat Z, Yousuf M, Castaldo G, Rastrelli L, Khan H. Virtual screening of natural products against Type II transmembrane serine protease (TMPRSS2), the priming agent of coronavirus 2 (SARS-CoV-2). Molecules. 2020 Jan;25(10):2271. doi: 10.3390/molecules25102271, PMID 32408547.

7. Solnier J, Fladerer JP. Flavonoids: A complementary approach to conventional therapy of COVID-19? Phytochem Rev. 2020 Sep 18:1-23. doi: 10.1007/s11101-020-09720-6, PMID 32982616.
8. McEwen BJ. The influence of herbal medicine on platelet function and coagulation: a narrative review. InSeminars in Thrombosis and Hemostasis 2015 Apr (Vol. 41, No. 03, pp. 300-314). Thieme Medical Publishers.
9. Boy HIA, Rutilla AJH, Santos KA, Ty AMT, Yu AI, Mahboob T, Tangpoong J, Nissapatorn V. Recommended medicinal plants as source of natural products: a review. Digit Chin Med. 2018 Jun 1;1(2):131-42. doi: 10.1016/S2589-3777(19)30018-7.
10. Ammakiw CL, Odiem MP. Availability, preparation and uses of herbal plants in Kalinga, Philippines. Eur Sci J. 2013 Nov 10;4:483-9.
11. Chegu K, Mounika K, Rajeswari M, Vanibala N, Sujatha P, Sridurga P, Reddy DB. *In vitro* study of the anticoagulant activity of some plant extracts. World J Pharm Pharm Sci. 2018 Mar 4;7(5):904-13.
12. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016;5:e47. doi: 10.1017/jns.2016.41, PMID 28620474.
13. Vallance TM, Ravishankar D, Albadawi DAI, Osborn HMI, Vaiyapuri S. Synthetic flavonoids as novel modulators of platelet function and thrombosis. Int J Mol Sci. 2019 Jan;20(12):3106. doi: 10.3390/ijms20123106, PMID 31242657.
14. Beretz A, Cazenave JP. The effect of flavonoids on blood-vessel wall interactions. Prog Clin Biol Res. 1988;280:187-200. PMID 3051026.
15. Lee CJ, Ansell JE. Direct thrombin inhibitors. Br J Clin Pharmacol. 2011 Oct;72(4):581-92. doi: 10.1111/j.1365-2125.2011.03916.x, PMID 21241354.
16. Ku SK, Kim TH, Bae JS. Anticoagulant activities of persicarin and isorhamnetin. Vascul Pharmacol. 2013 Apr 1;58(4):272-9. doi: 10.1016/j.vph.2013.01.005, PMID 23391847.
17. Kim DC, Ku SK, Bae JS. Anticoagulant activities of curcumin and its derivative. BMB Rep. 2012;45(4):221-6. doi: 10.5483/bmbrep.2012.45.4.221, PMID 22531131.
18. Bijak M, Bobrowski M, Borowiecka M, Podsędek A, Golański J, Nowak P. Anticoagulant effect of polyphenols-rich extracts from black chokeberry and grape seeds. Fitoterapia. 2011 Sep 1;82(6):811-7. doi: 10.1016/j.fitote.2011.04.017, PMID 21596108.
19. Ayodele OO, Onajobi FD, Osoniyi O. *In vitro* anticoagulant effect of Crassocephalum crepidioides leaf methanol extract and fractions on human blood. J Exp Pharmacol. 2019;11:99-107. doi: 10.2147/JEP.S218261, PMID 31564995.
20. Edziri H, Jaziri R, Haddad O, Anthonissen R, Aouni M, Mastouri M, Verschaeve L. Phytochemical analysis, antioxidant, anticoagulant and *in vitro* toxicity and genotoxicity testing of methanolic and juice extracts of Beta vulgaris L. S Afr J Bot. 2019 Nov 1;126:170-5. doi: 10.1016/j.sajb.2019.01.017.
21. Rehman AA, Riaz A, Asghar MA, Raza ML, Ahmed S, Khan K. *In vivo* assessment of anticoagulant and antiplatelet effects of Syzygium cumini leaves extract in rabbits. BMC Complement Altern Med. 2019 Dec;19(1):236. doi: 10.1186/s12906-019-2661-y, PMID 31481052.
22. Félix-Silva J, Souza T, Camara RB, Cabral B, Silva-Júnior AA, Rebecchi IM, Zucolotto SM, Rocha HA, Fernandes-Pedrosa Mde F. *In vitro* anticoagulant and antioxidant activities of *Jatropha gossypiifolia* L. (Euphorbiaceae) leaves aiming therapeutical applications. BMC Complement Altern Med. 2014;14:405. doi: 10.1186/1472-6882-14-405. PMID 25328027.
23. Rodrigues CF, Gaeta HH, Belchor MN, Ferreira MJ, Pinho MV, Toyama Dde O, Toyama MH. Evaluation of potential thrombin inhibitors from the white mangrove (Laguncularia racemosa (L.) CF Gaertn.). Mar Drugs. 2015 Jul;13(7):4505-19. doi: 10.3390/md13074505, PMID 26197325.
24. Pawlaczyk I, Czerchawski L, Kuliczkowski 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. Thromb Res. 2011 Apr 1;127(4):328-40. doi: 10.1016/j.thromres.2010.11.031, PMID 21172723.
25. Khouya T, Ramchoun M, Hmidani A, Amrani S, Harnafi H, Benlyas M, Filali Zegzouti YF, Alem C. Anti-inflammatory, anticoagulant and antioxidant effects of aqueous extracts from Moroccan thyme varieties. Asian Pac J Trop Biomed. 2015 Aug 1;5(8):636-44. doi: 10.1016/j.apjtb.2015.05.011.

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