REVIEW ARTICLE

Anticoagulant Activity in Medicinal Plants: A Systematic and Bibliometric Review Over 10 Years (2011-2021)

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ABSTRACT

Anticoagulants are helpful as treatment for coagulation disorders. Medicinal plants have been demonstrated to be part of history as a traditional treatment for this disorder, and these plants have anticoagulant properties. Hence, the goal of this study is to review the available publications on anticoagulant activity in medicinal plants from the year 2011 until 2021 using Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines and bibliometric analysis. This review was performed based on the PRISMA guidelines and VOSviewer as a bibliometric analysis tool, using three search databases which were PubMed, MyMedR, and ScienceDirect. The findings of this study revealed that 27 articles met the inclusion criteria and focused on anticoagulant activity in medicinal plants. In each study, anticoagulant properties in medicinal plants were addressed. Meanwhile, the results of the bibliometric analysis demonstrated that China has the most publications for anticoagulant activity in medicinal plants and had the most collaboration among institutes in their country. For the most used keywords used by the author, the word "anticoagulant activity" came on top of the results. To conclude, this study can contribute to the field of study as it helps combine the data related to anticoagulant activities in medicinal plants.

INTRODUCTION

Both arterial and venous thromboembolism may be prevented and treated using anticoagulants, which are the main treatment. A variety of anticoagulants interfere with the coagulation process in different ways.[1,2] Instead of breaking up clots that already exist, this category of drugs reduces the development of thrombosis and slows or stops the spread of existing clots.[3-5] Because of their accessibility, cost, and safety, medicinal plants are an excellent alternative to traditional treatment.[6,7] The proper care and use of medicinal plants used to treat coagulation disorders is essential to prevent the development of toxicity that could bring damage to human health.[8,9] Some bioactive chemicals extracted from medicinal plants have been shown in prior research to have anticoagulant, antiplatelet, and antithrombotic properties.[10]

Moreover, a systematic review commonly put all the evidence together to answer a question that has already been set up. This includes finding all the primary research relevant to the review question, evaluating this research, and putting the findings together.[11-13] Besides, a common and reliable way to look at and analyse a lot of scientific data is through bibliometric analysis. It provides assistance in comprehending the ways in which a particular field has evolved over the course of time and sheds light on new aspects of that field.[14] This paper systematically reviewed and performed bibliometric analysis for papers published from the year 2011 until 2021. Overall, based on the search terms used, four review papers were published during this period. It needs to be acknowledged that the factor of geographical source of plant materials can make safety evaluation challenging. Different countries may have different ways of managing and utilizing the medicinal plants' materials. The analysis of harmful occurrences associated with the use of herbal medicines is significantly more complex than the usual medicines,

making the assessment of their safety very crucial. Thus, the research questions for this paper are:

i. How many reports have been published that are linked to anticoagulant activity in medicinal plants?
ii. Which country published the most literature about anticoagulant activity in the medicinal plants from the year 2011 until 2021?
iii. How many institutes did a collaboration on anticoagulant activity in the medicinal plants?
iv. What are the most frequently used keywords by authors?

There were 197 publications linked to anticoagulant activity in medicinal plants with China publishing the most literature about anticoagulant activity in medicinal plants from the year 2011 until 2021. Also, institutes in China did the most collaboration on anticoagulant activity in the medicinal plants. Moreover, 'anticoagulant activity' is the most used keyword in the publications during this selected period. Therefore, this study aims to review the available publications on anticoagulant activity in medicinal plants from the year 2011 until the year 2021 using Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines and bibliometric analysis.

REVIEW METHODOLOGY

Search Strategy and Study Design

This review was performed based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines using the following search databases: PubMed, MyMedR, and ScienceDirect.[15] The search terms used were "anticoagulant and plant," "anticoagulant and medicinal plant," "anticoagulant activity and medicinal plant," and "anticoagulant and herbal." The techniques of searching were (All fields) for PubMed, (All Fields – MyJurnal) for MyMedR, and (Terms in title, abstract or author-specified keywords) for ScienceDirect. Besides, there were limitations about language, article type, and date of publication. The results were restricted to literature written in English language only. Moreover, the article type was restricted to only books and documents, clinical trials, meta-analysis, and randomized controlled trials for PubMed, and only research articles and book chapters for ScienceDirect. The literature search's timeframe covered the past ten years, from 2011 until 2021, to ensure that recent and effective medicinal plants have anticoagulant properties were highlighted.

Eligibility and Study Selection

The abstracts from the studies were critically reviewed for relevancy to anticoagulant activity in medicinal plants. In this study, the criteria for including articles for review were literature relevant to anticoagulant activity in medicinal plants, articles available in full-text access or open access, type of publication, written in English language and studies that reported in human plasma as subjects. Next, articles available in the full text were further scrutinized. The exclusion criteria for this study were studies that include plasma of non-human subjects. In addition, books, systematic reviews, review papers, case reports, and conference abstracts were excluded from this study. Articles that were not relevant to the anticoagulant activity in medicinal plants were also excluded. This criterion was examined after the title and abstract of the articles had been examined thoroughly.

Initially, there were a total of 197 documents resulting from the four search terms used. However, this also included articles that were duplicates. Using EndNote version X20.2.1 software, 82 duplicated articles were eliminated. After duplicates were removed, the remaining 115 articles were screened by title and abstract, or full-text access. There were nine books and 44 articles being removed as they had no full-text availability. Next, 62 articles were assessed against the eligibility criteria. The reasons for exclusion were the type of publication, studies that have no relevance to anticoagulant activity in medicinal plant, and studies that do not report in human plasma. The flow diagram of the literature search based on the PRISMA guidelines is shown in Figure 1.

Data Extraction and Synthesis of Findings

Data from 27 studies included for review were extracted into the table of evidence. The information includes the name of authors, year of publication, study design, population of the study, and anticoagulant activity in the medicinal plants.

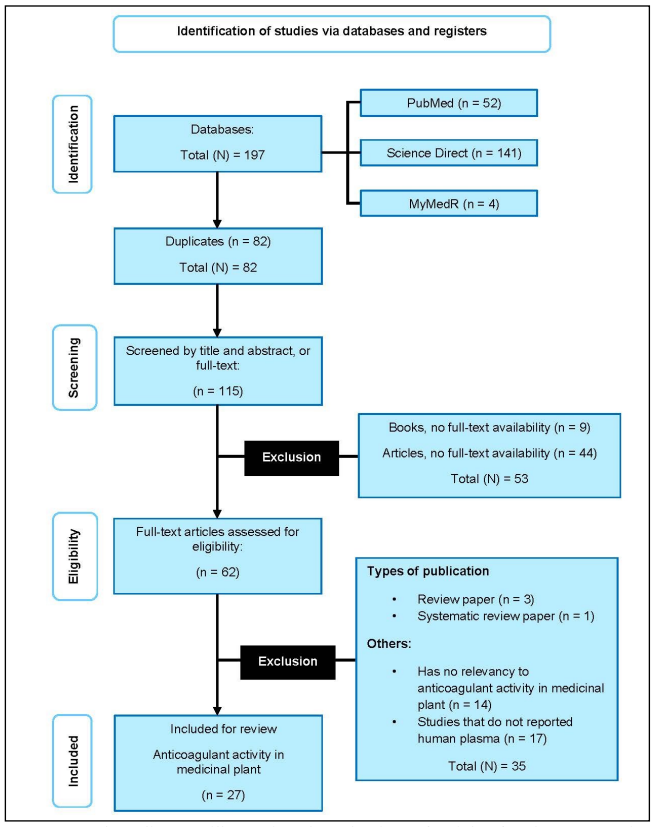

Figure 1. Flow diagram illustrating the selection of articles for the systematic review based on Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.

RESULTS AND DISCUSSION

Study Characteristics

There were 197 publications identified from the initial search. The search terms "anticoagulant and plant," "anticoagulant and medicinal plant," "anticoagulant activity and medicinal plant," and "anticoagulant and herbal" were applied to these three databases, PubMed, MyMedR, and ScienceDirect. By selecting various synonymous, it can be ensured that the topic within this particular field of interest was covered to the greatest extent possible. Also, by including more papers that cover the same subject, bias could be avoided. In addition, as the key terms may be restricted in some countries, as many countries as possible can be included, hence preventing bias in this report. As a result, there were 52 articles from PubMed, 141 in Science Direct, and four in MyMedR. The year of publication of the articles ranged from 2011 to 2021, with English language as limitation. Using EndNote version X20.2.1 software, 82 duplicated articles were eliminated.

After the first exclusion, the rest of the articles (115) were screened by title, abstract and full text. In the first exclusion, 53 articles were also removed. Next, the remaining 62 publications were further filtered down based on specific eligibility criteria. Four articles were removed because of their type of publications. These studies involve three review papers and one systematic review paper. Another 14 articles that have no relevance to anticoagulant activity in medicinal plants were also removed. Another exclusion criterion was if the study that does not report human plasma which involves 17 studies. Hence, they were excluded from this review. Overall, the second exclusion stage generated the removal of 35 publications. Finally, 27 remaining articles were eligible for analysis, focusing on anticoagulant activity in medicinal plants.

Main Findings

In all included studies, the presence of anticoagulant activity in medicinal plants was acknowledged (Table 1). Most of the study designs for the included studies were case-control, which is known as a type of observational study.[16,17] Four out of 27 studies did not demonstrate the presence of anticoagulant activity in medicinal plants.[18-21] One of the studies resulted in no changes in prothrombin time (PT) and activated partial thromboplastin time (aPTT) tests, hence indicating that no anticoagulant activity was present in *Beta vulgaris* L. plant.[18] Another study that used similar *Beta vulgaris* L. found anticoagulant activities in their subjects however the reason for this contrasted result could not be identified.[22]

One study reported that there was no presence of anticoagulant impact since the assessment of *Cinnamomum zeylanicum*'s anticoagulant impact remains unchanged. Over the course of the study, they measured the anticoagulant impact by doing a series of prothrombin time (PT/INR) tests.[19] Compared to *Cassia cinnamon*, *Cinnamomum zeylanicum* has far lower quantities of coumarin.[23] Coumarin is a naturally occurring potent anticoagulant.[24,25] Moreover, the result of one past study demonstrated that *Operculina macrocarpa* has no anticoagulant effect as it did not increase the PT and

aPTT in human plasma.[20] Besides, based on the results, it was also discovered that *Curcuma longa*, *Angelica sinensis* and *Panax ginseng* has no anticoagulant impact by using the PT and aPTT assays.[21]

Table I. Table of main findings for all included studies.

References	Study design	Population of study	Activity of anticoagulant in medicinal plants
Raubenheimer et al. (2017) [18]	Randomized Double-blind Placebo-controlled Crossover	Total = 12 Male, healthy adults = 5 Female, healthy adults = 7	*Beta vulgaris L.*: No presence of anticoagulant activity
Ranasinghe et al. (2017) [19]	Clinical trial	Total = 28 Male, healthy adults = 14 Female, healthy adults =14	*Cinnamomum zeylanicum*: No presence of anticoagulant activity
Dakshayani et al. (2019) [26]	Case-control	Total = 10 Positive controls = 5 Negative controls = 5	*Selaginella bryopteris* (Sanjeevini): Anticoagulant activity is present
da Luz et al. (2021) [27]	Case-control	Total = 15 Group 1, normal controls = 3 Group 2, treated with CELR = 3 Group 3 treated with CELR = 3 Group 4, treated with ALR = 3 Group 5. treated with ALR = 3	*Licania rigida*: Anticoagulant activity is present
Skalski et al. (2021) [28]	Case-control	Total = 6 Non-smoking males and females = 6	*Orobanche caryophyllacea*, *Phelipanche arenaria*, and *P. ramosa*: Anticoagulant activity is present
Hmidani et al. (2019) [29]	Case-control	Not stated	*Thymus atlanticus*: Anticoagulant activity is present
Siritapetawee et al. (2020) [30]	Case-control	Total = 10 Healthy volunteers = 10	*Euphorbia resinifera*: Anticoagulant activity is present
de Araujo et al. (2021) [31]	Case-control	Healthy donors of the Hemotherapy Center of Ceará, Brazil	*Caesalpinia ferrea*: Anticoagulant activity is present
Edziri et al. (2019) [22]	Case-control	Healthy volunteers	*Beta vulgaris L.*: Anticoagulant activity is present
Madeira et al. (2018) [32]	Case-control	Healthy donors of the Hemotherapy Center of Ceará, Brazil	*Genipa americana*: Anticoagulant activity is present
Souza et al. (2015) [33]	Case-control	Healthy donors of the Hemotherapy Center of Ceará, Brazil	*Geoffroea Spinosa*: Anticoagulant activity is present
Nguyen et al. (2020) [34]	Case-control	Healthy volunteers	*Canna edulis* Ker Gawl: Anticoagulant activity is present
Hamed et al. (2020) [35]	Case-control	Not stated	*Ficus carica*: Anticoagulant activity is present
Rahman et al. (2020) [36]	Case-control	Total = 10 Male, healthy = 10	*Delonix regia (Bojer ex Hook.) Raf.*, *Cassia fistula L.* and *Lagerstroemia speciosa L.*: Anticoagulant activity is present
Kolodziejczyk-Czepas et al. (2020) [37]	Case-control	Healthy volunteers	*Uncaria tomentosa*: Anticoagulant activity is present
Cotabarren et al. (2020) [38]	Case-control	Total = 5	*Geoffroea decorticans*: Anticoagulant activity is present
Juszczak et al. (2021) [39]	Case-control	Non-smoking male and female donors	*Elaeagnus rhamnoides (L.) A. Nelson*: Anticoagulant activity is present
Magalhães et al. (2010) [40]	Case-control	Healthy donors	*Marsypianthes chamaedrys*: Anticoagulant activity is present
Jedrejek et al. (2019) [41]	Case-control	Regular, medication-free donors from a blood bank and Medical Center in Łódź (Poland)	*Taraxacum officinale:* Anticoagulant activity is present
Lis et al. (2018) [42]	Case-control	Regular, medication-free donors from a blood bank and Medical Center in Łódź (Poland)	*Taraxacum officinale:* Anticoagulant activity is present
Hamedi et al. (2019) [43]	Case-control	Male volunteers Female volunteers	*Diospyros lotus*: Anticoagulant activity is present
Luz et al. (2013) [44]	Case-control	Not stated	*Moringa oleifera*: Anticoagulant activity is present
Byankina (Barabanova) et al. (2013) [45]	Case-control	Healthy volunteers	*Tichocarpus crinitus*: Anticoagulant activity is present
Pierdoná et al. (2014) [20]	Case-control	Healthy volunteers	*Operculina macrocarpa*: No presence of anticoagulant activity
Silva et al. (2012) [46]	Case-control	Healthy volunteers	*Bauhinia forficata*: Anticoagulant activity is present
Fung et al. (2017) [21]	Randomized Double-blind Placebo-controlled trial	Total = 75 Healthy volunteers with *Curcuma longa* herbal product = 25 Healthy volunteers with *Angelica sinensis* herbal product = 25 Healthy volunteers with *Panax ginseng* herbal product = 25	*Curcuma longa*, *Angelica sinensis* and *Panax ginseng*: No presence of anticoagulant activity
Paul et al. (2015) [47]	Case-control	Male, healthy adults Female, healthy adults	*Diplazium esculentum (retz.) sw.*: Anticoagulant activity is present

Bibliometric Analysis

In this study, 115 documents linked to anticoagulant activity in medicinal plants were retrieved from PubMed, MyMedR, and ScienceDirect databases. These documents have been subjected to bibliometric analysis after they have been filtered by removing the duplicates. All documents from each database were downloaded and being collected in a csv (comma-separated value) format of file. Csv is one of the file formats that can be used and read by the VOSviewer, which is a software created to analyse bibliometric connections. Some of the data retrieved from these three databases: PubMed, MyMedR, and ScienceDirect, were distinct from one another.

For the PubMed database, the data retrieved was PubMed unique identifier (PMID) number, publication type, title of publication, author names, title of source, year published, digital object identifier (DOI) number, affiliation of the authors, author keywords, and references for the publication. Next, data retrieved in ScienceDirect database was publication type, title of publication, author names, title of source, year published, digital object identifier (DOI) number, affiliation of the authors, author keywords, and references for the publication. Besides, for the MyMedR database, the data retrieved was title of publication, author names, title of source, year published, affiliation of the authors, author keywords, and references for the publication.

Countries

Figure 2 was obtained using VOSviewer. This figure shows the analysis that was conducted, from the year 2011 until 2021, the most active country publishing in anticoagulant activity in medicinal plants was China which covered 19.76% of the total publications, followed by the United Kingdom and the United States, which covered 12.79% and 11.62%, discretely. In the last decade, China's research and development spending has increased by around 20% every year.[48,49] Currently, China has recorded 32 patents, and Guangzhou Hongchang Biotechnology Co Ltd as the top owner, has allotted two patent records. Revolutionary treatments in China that are still active include *Coptosapelta diffusa* polysaccharide, glossy privet flower polysaccharide, and oak bark volatile oil as anticoagulants. Furthermore, Kang Wenyi was acknowledged as the highest inventor of patent records in China and has contributed four documents to the country that involve anticoagulants such as glossy privet flower polysaccharide, blackberry seed, blackberry seed polysaccharides, and filamental flowering crab extract.[50]

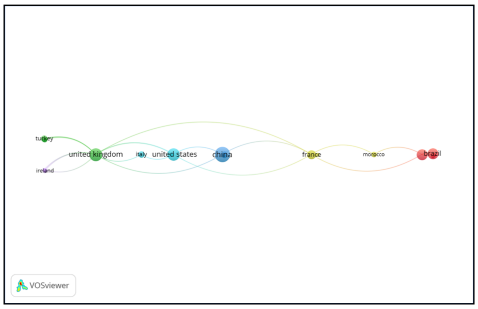

Figure 2. Top 20 countries published the most literature.

Also, a 2011 survey by the British Royal Society revealed that, between 2004 and 2008, China generated 10% of the world's published scientific publications, placing it second only to the United States in terms of scientific production.48 This may be the reason why China is performing better than other countries in research of anticoagulant activity in medicinal plants. The increase in anticoagulant research in China has the potential to yield not just a potent revolutionary treatment, but also a better understanding of anticoagulant studies among researchers and improved clinical procedures of anticoagulant therapy in the future. Table 2 shows the top 20 countries published the most literature about anticoagulant activity in medicinal plants from the year

Table II. Top 20 countries contributed to the most literature.

Country	Frequency	% (N=86)
United Kingdom	11	12.79
France	6	6.97
Germany	8	9.30
United States	10	11.62
China	17	19.76
Hungary	1	1.16
Ireland	1	1.16
Malta	1	1.16
Sri Lanka	2	2.32
Turkey	3	3.48
Brazil	8	9.30
Indonesia	1	1.16
Iran	3	3.48
Italy	3	3.48
Malaysia	3	3.48
Morocco	2	2.32
Belgium	1	1.16
Bulgaria	2	2.32
Egypt	2	2.32
Mexico	1	1.16
Total	**86**	**100.00**

Institution

Figure 3 shows the institutions that have the most collaboration in publishing articles regarding anticoagulant activity in medicinal plants from year 2011 until year 2021, with at least one document for each institution. The Hubei Minzu University, Zhengzhou University, Foshan Women and Children Hospital, Henan University of Chinese Medicine, Jiangxi University of Technology High School, Henan University of Science and Technology, and Nanchang University are all located in China.

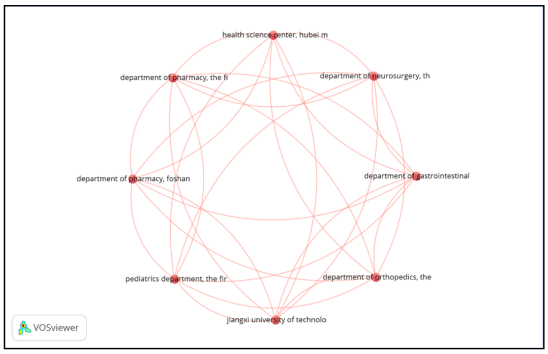

Figure 3. Network visualization map of the most collaborated institutions.

Keywords Analysis

From Figure 4, the connection between most of the keywords used by the authors is shown. The size of the words revealed the frequency of the words that are related to anticoagulant and plant being used. The hue of the words indicates that the subject has a common vocabulary of terms. This may be observed in Figure 4, as an example, the word coagulation time and plant polysaccharides have light blue colour. Table 3 shows anticoagulant activity is the most used keywords and has the largest size, with the frequency of 10.94% that covered all the publications.

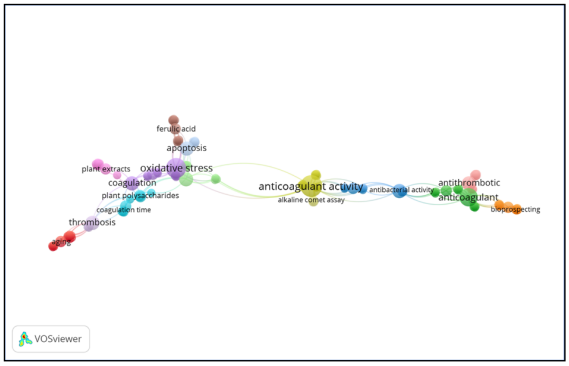

Figure 4. Network visualization map of author keywords.

Following anticoagulant activity is oxidative stress and warfarin, which both covered 9.8%, simultaneously. Based on the table, the word antithrombic is part of the top 20 keywords used by the author. It might appear to be related to the word anticoagulant as it is also one of the activities present in medicinal plants. In addition, there are anticoagulant and anticoagulants words in the table. This may indicate that there is a possibility of a plural existence that the author wanted to express in specific occurrence of situations in their papers.

Table III. Top 20 author keywords with the most frequency.

Author keywords	Frequency	% (N= 64)
anticoagulants	4	6.25
warfarin	6	9.38
anticoagulant activity	7	10.94
oxidative stress	6	9.38
anticoagulant	5	7.81
molecular docking	2	3.13
thrombosis	3	4.69
apoptosis	3	4.69
antithrombotic	3	4.69
biocides	3	4.69
silver nanoparticles	3	4.69
haemostasis	3	4.69
aging	2	3.13
interaction	3	4.69
meta-analysis	3	4.69
alanine	1	1.56
betaine	1	1.56
biochemistry	1	1.56
coagulation	3	4.69
ferulic acid	2	3.13
Total	**64**	**100.00**

CONCLUSIONS AND FUTURE PERSPECTIVES

By reviewing the available publications on anticoagulant activity in medicinal plants from the year 2011 until 2021 using Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines and bibliometric analysis, this study has established that there were 115 reports have been published (following the inclusion criteria) that are linked to anticoagulant activity in medicinal plants. China was the country that published the most literature about anticoagulant activity in the medicinal plants from the year 2011 until 2021. Besides, China is putting a lot of emphasis on alternative health care. China's enthusiasm in complimentary medicines

research is well-known. They have an abundance of atypical complimentary drugs practices and when it comes to herbal-based complementary medicines, they have numerous success stories. "Anticoagulant activity", "oxidative stress" and "warfarin" were the top three most frequently used keywords by authors.

In this study, we have shown that the availability of anticoagulant activities was addressed, with only a few of them showing contrasted results with no presence of anticoagulant properties in the plants. Researchers who plan to start or pursue research on medicinal plants or anticoagulants will benefit from this study. Moreover, medicinal plants are better for humans than toxic medicines because they have less toxicity effects. Furthermore, this study is the first paper using the systematic review and bibliometric analysis approach to investigate the anticoagulant activity in medicinal plants. The impact of this paper on this field of study is it can be used as a reference to support the occurrence of anticoagulant properties in medicinal plants. Further studies are required to highlight the mechanism of action of medicinal plants, along with the toxicity and cytotoxicity effects of medicinal plant components and preparation of medicinal plant extract on human blood. Overall, the findings exhibit contrasting results between a medicinal plant, *Beta vulgaris* L. It is advisable to recommend further studies to identify why this plant exhibits different values in blood clotting test results.

REFERENCES

1. Myers K, Lyden AE. A Review on the New and Old Anticoagulants. Orthopedic nursing 2019; 38(1), 43-52.
2. Chan NC, Eikelboom JW, Weitz JI. Evolving treatments for arterial and venous thrombosis: Role of the direct oral anticoagulants: Role of the direct oral anticoagulants. Circulation Research 2016; 118 (9):1409–24.
3. LaPelusa A, Dave HD. Physiology, Hemostasis. Florida: StatPearls Publishing, 2022.
4. Smith SA, Travers RJ, Morrissey JH. How it all starts: Initiation of the clotting cascade. Critical Reviews in Biochemistry and Molecular Biology 2015; 50(4):326–36.
5. Abrams A, Lammon C, Pennington S. Clinical Drug Therapy: Rationales for Nursing Practice. 9th ed. Pennsylvania: Wolters Kluwer/Lippincott Williams & Wilkins, 2009.
6. Osunsanmi FO, Zaharare GE, Oyinloye BE, et al. Antithrombotic, anticoagulant and antiplatelet activity of betulinic acid and 3β-acetoxybetulinic acid from melaleuca bracteata 'revolution gold' (Myrtaceae) Muell Leaf. Tropical Journal of Pharmaceutical Research 2019; 17(10):1983-89.
7. Osunsanmi FO, Soyinbe OS, Ogunyinka IB, et al. Antiplatelet aggregation and cytotoxic activity of betulinic acid and its acetyl derivative from Melaleuca bracteata. J Med Plant 2015; 9(22):647-854.
8. Sofowora A, Ogunbodede E, Onayade A. The role and place of medicinal plants in the strategies for disease prevention. African Journal of Traditional, Complementary and Alternative Medicines 2013; 10 (5).
9. Mensah MLK, Komlaga G, Forkuo AD, Firempong C, et al. Toxicity and safety implications of herbal medicines used in Africa. Herbal Medicine 2019.
10. Klafke JZ, da Silva MA, Rossato MF, et al. Antiplatelet, Antithrombotic, and Fibrinolytic Activities of Campomanesia xanthocarpa. Evidence-Based Complementary and Alternative Medicine 2012; 2012:1–8.
11. Pollock A, Berge E. How to do a systematic review. International Journal of Stroke 2017; 13(2): 138-56.
12. Borah R, Brown AW, Capers PL, et al. Analysis of the time and workers needed to conduct systematic reviews of medical interventions using data from the Prospero Registry. BMJ Open 2017; 7(2).
13. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. Public Library of Science Medicine 2009; 6(7).
14. Donthu N, Kumar S, Mukherjee D, et al. How to conduct a bibliometric analysis: An overview and guidelines. Journal of Business Research 2021; 133: 285-96.

15. Page MJ, McKenzie JE, Bossuyt PM, et al. The Prisma 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021; 372(71).
16. Setia MS. Methodology Series Module 2: Case-control Studies. Indian Journal of Dermatology 2016; 61 (2):146-51.
17. Song JW, Chung KC. Observational Studies: Cohort and Case-Control Studies. Plastic and Reconstructive Surgery 2010; 126(6):2234-2242.
18. Raubenheimer K, Hickey D, Leveritt M, et al. Acute Effects of Nitrate-Rich Beetroot Juice on Blood Pressure, Hemostasis and Vascular Inflammation Markers in Healthy Older Adults: A Randomized, Placebo-Controlled Crossover Study. Nutrients, 2017; 9(11).
19. Ranasinghe, P., Jayawardena, R., Pigera, S., Wathurapatha, W., Weeratunga, H., & Premakumara, G. et al. (2017). Evaluation of pharmacodynamic properties and safety of Cinnamomum zeylanicum (Ceylon cinnamon) in healthy adults: a phase I clinical trial. BMC Complementary and Alternative Medicine, 17(1).
20. Pierdoná TM, Lima NR, Rodrigues RCM, et al. The Operculina macrocarpa (l.) urb. (jalapa) tincture modulates human blood platelet aggregation. Journal of Ethnopharmacology 2014; 151(1):151–7.
21. Fung FY, Wong WH, Ang SK, et al. A randomized, double-blind, placebo- controlled study on the anti-haemostatic effects of Curcuma longa, Angelica sinensis and Panax ginseng. Phytomedicine 2017; 32:88–96.
22. Edziri H, Jaziri R, Haddad O, et al. Phytochemical analysis, antioxidant, anticoagulant and in vitro toxicity and genotoxicity testing of methanolic and juice extracts of Beta vulgaris L. South African Journal of Botany 2019; 126:170–175.
23. Archer AW. Determination of cinnamaldehyde, coumarin and cinnamyl alcohol in cinnamon and cassia by high-performance liquid chromatography. J Chromatography A 1988; 447:272–6.
24. Sharifi-Rad J, Cruz-Martins N, López-Jornet P, et al. Natural coumarins: Exploring the pharmacological complexity and underlying molecular mechanisms. Oxidative Medicine and Cellular Longevevity 2021; 2021.
25. Venugopala KN, Rashmi V, Odhav B. Review on natural coumarin lead compounds for their pharmacological activity. BioMed Research International 2013; 2013.
26. Dakshayani SS, Marulasiddeshwara MB, Sharath Kumar MN, et al. Antimicrobial, anticoagulant and antiplatelet activities of green synthesized silver nanoparticles using Selaginella (Sanjeevini) plant extract. International Journal of Biological Macromolecules 2019; 131:787-97.
27. da Luz J, do Nascimento T, Araujo-Silva G, et al. Licania rigida Benth leaf extracts: Assessment of toxicity and potential anticoagulant effect. South African Journal of Botany 2021; 139:217-25.
28. Skalski B, Pawelec S, Jedrejek D, et al. Antioxidant and anticoagulant effects of phenylpropanoid glycosides isolated from broomrapes (Orobanche caryophyllacea, Phelipanche arenaria, and P. ramosa). Biomedicine & Pharmacotherapy 2021;139.
29. Hmidani A, Bouhlali EDT, Khouya T, et al. Effect of extraction methods on antioxidant and anticoagulant activities of Thymus atlanticus aerial part. Scientific African 2019; 5.
30. Siritapetawee J, Khunkaewla P, Thumanu K. Roles of a protease from Euphorbia resinifera latex in human anticoagulant and antithrombotic activities. Chemico-biological Interactions 2020; 329(109223).
31. de Araujo DF, Madeira J da C, Cunha AP, et al. Structural characterization of anticoagulant and antithrombotic polysaccharides isolated from Caesalpinia ferrea stem barks. International Journal of Biological Macromolecules 2021; 175:147–55.
32. Madeira JC, da Silva GVL, Batista JJ, et al. An arabinogalactan-glycoconjugate from Genipa americana leaves present anticoagulant, antiplatelet and antithrombotic effects. Carbohydrate Polymers 2018; 202:554–62.
33. Souza ROS, Assreuy AMS, Madeira JC, Chagas FDS, Parreiras LA, Santos GRC, et al. Purified polysaccharides of Geoffroea spinosa barks have anticoagulant and antithrombotic activities devoid of hemorrhagic risks. Carbohydrate Polymers 2015; 124:208–15.

34. Nguyen TMH, Le HL, Ha TT, et al. Inhibitory effect on human platelet aggregation and coagulation and antioxidant activity of C. edulis Ker Gawl rhizome and its secondary metabolites. Journal of Ethnopharmacology 2020; 263(113136):113136.
35. Hamed MB, El-Badry MO, Kandil EI, et al. A contradictory action of procoagulant ficin by a fibrinolytic serine protease from Egyptian Ficus carica latex. Biotechnology Reports 2020; 27 (e00492).
36. Rahman FB, Ahmed S, Noor P, et al. A comprehensive multi-directional exploration of phytochemicals and bioactivities of flower extracts from Delonix regia (Bojer ex Hook.) Raf., Cassia fistula L. and Lagerstroemia speciosa L. Biochemistry and Biophysics Reports 2020; 24:100805.
37. Kolodziejczyk-Czepas J, Ponczek M, Sady-Janczak M, et al. Extracts from Uncaria tomentosa as antiplatelet agents and thrombin inhibitors - The in vitro and in silico study. Journal of Ethnopharmacology 2021; 267(113494).
38. Cotabarren J, Broitman DJ, Quiroga E, et al. GdTI, the first thermostable trypsin inhibitor from Geoffroea decorticans seeds. A novel natural drug with potential application in biomedicine. International Journal of Biological Macromolecules 2020;148: 869–79.
39. Juszczak M, Kluska M, Skalski B, et al. Multidirectional effects of saponin fraction isolated from the leaves of sea buckthorn Elaeagnus rhamnoides (L.) A. Nelson. Biomedicine & Pharmacotherapy 2021; 137(111395).
40. Magalhães A, Santos GBD, Verdam MCDS, et al. Inhibition of the inflammatory and coagulant action of Bothrops atrox venom by the plant species Marsypianthes chamaedrys. Journal of Ethnopharmacology 2011; 134(1):82–8.
41. Jedrejek D, Lis B, Rolnik A, et al. Comparative phytochemical, cytotoxicity, antioxidant and haemostatic studies of Taraxacum officinale root preparations. Food and Chemical Toxicology 2019; 126:233–47.
42. Lis B, Jędrejek D, Stochmal A, et al. Assessment of effects of phenolic fractions from leaves and petals of dandelion in selected components of hemostasis. Food Research International 2018; 107:605–12.
43. Hamedi S, Shojaosadati SA. Rapid and green synthesis of silver nanoparticles using Diospyros lotus extract: Evaluation of their biological and catalytic activities. Polyhedron 2019; 171:172–80.
44. Luz L de A, Silva MCC, Ferreira R da S, et al. Structural characterization of coagulant Moringa oleifera Lectin and its effect on hemostatic parameters. International Journal of Biological Macromolecules 2013; 58:31–6.
45. Byankina Barabanova AO, Sokolova EV, Anastyuk SD, et al. Polysaccharide structure of tetrasporic red seaweed Tichocarpus crinitus. Carbohydrate Polymers 2013; 98(1):26–35.
46. Silva MCC, Santana LA, Mentele R, et al. Purification, primary structure and potential functions of a novel lectin from Bauhinia forficata seeds. Process Biochemistry 2012; 47(7):1049–59.
47. Paul B, Bhuyan B, Purkayastha DD, et al. Green synthesis of silver nanoparticles using dried biomass of Diplazium esculentum (retz.) sw. and studies of their photocatalytic and anticoagulative activities. Journal of Molecular Liquids 2015; 212:813–7.
48. Qiu J. China's funding system and research innovation. National Science Review 2014; 1(1): 161 -3.
49. Xie Y, Zhang C, Lai Q. China's rise as a major contributor to science and technology. PProceedings of the National Academy of Sciences of the United States of America 2014; 111(26):9437 –42.
50. Patent Analysis [Online]. Available at: https:// www.lens.org/lens/search/patent/analysis?q= (anticoagulant%20plant) &p=0&n=10&s=_score&d=% 2B&f=false&e=false&l=en&authorField=author&d ateFilterField=publishedDate&orderBy=% 2B_score&presentation=false&preview=true&stem med=true&useAuthorId=false&j.must=CN. Accessed December 30, 2022.