Review Article

Anticoagulant Properties of Medicinal Plants of Asteraceae: A Systematic Review

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ABSTRACT

The *Asteraceae* family is considered to be the largest family of flowering plants. Asteraceae includes annuals, perennials, ground covers, vines, and shrubs. Plants belonging to this family are used as a conventional medicine all over the world, and it has been shown to have a range of biological benefits, including anti-inflammatory, antioxidant, and anticoagulant properties. Plants from the *Asteraceae* are believed to be rich in flavonoids, coumarins, and other constituents that help in the coagulation process. This systematic review generally aims to provide an overview concerning the anticoagulant activity of different medicinal plants under the family of *Asteraceae*. After rigorous screening using combined *SPIDER* and *PICO* strategies, 17 experimental studies with Asteraceae plants showing anticoagulant activity were included. The different plants from the family were extracted using water, methanol, ethanol, and hexane method. Anticoagulant activity of different plants from the *Asteraceae* family was determined by performing tests and monitoring activated partial thromboplastin time and prothrombin time *in vitro* and *in vivo* to assess the intrinsic and extrinsic pathway. Moreover, the presence of coumarin, flavonoids, and polysaccharides significantly increased the aPTT and PT. Thus, these results suggest that the chemical constituents of *Asteraceae* plants may have the potential to prevent or improve thrombosis by inhibiting platelet activation and blood coagulation.

Key words: Asteraceae, Anticoagulant activity, Phytochemical, Activated partial thromboplastin time, Prothrombin time.

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INTRODUCTION

At present, the world is exposed to different kinds of diseases. The most common disease that affects a lot of people is those diseases that are related to blood or heart or also called for diseases of the blood circulation system. These kinds of diseases cause high mortality rates that develop in middle to low-income countries all over the world.[1] An example of this is venous thrombosis that occurs annually worldwide, 1 out of 1000 adults are affected.[2] Next is the thromboembolic disease which continues to be the cause of death throughout the world.[3] Thrombosis is closely related to activating platelet adhesion, aggregation, secretion functions, and activation of the intrinsic and extrinsic coagulation systems, which cause blood coagulation and fibrin formation.[4]

In addition, coronary disease is the most common and the most frequent disease that is prominent in the world because it can be easily accumulated by everyone, especially adults. If this is left untreated, this might lead to a heart attack. A heart attack is caused by the formation of a clot in the blood vessels or the heart, with this, it was recommended to take anticoagulant drugs to reduce the formation of a blood clot. According to the Centers for Disease Control and Prevention (2020), a heart attack occurs every 40 sec in the United States." Every year, 805,000 people in the United States had a heart attack, with 605,000 of them experiencing it for the first time. Around 12% of people who have a heart

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attack die as a result of it.[5] In the Philippines, it was stated by the World Health Organization (2018) that the Philippines has 19.83% (120,800) deaths because of coronary heart disease, and the rate adjusted 197.08 per 100,000 populations.[6]

The treatment of different kinds of diseases stated involves agents with thrombolytic, anticoagulant, and antiplatelet activities.[7] It was also stated that anticoagulants play an important role in treating and preventing diseases that involve blood thickening. Anticoagulants are medications that slow down the body's clotting mechanism Thus, anticoagulants are present not only in medications and narcotics but also in herbal plants and medicines. This is used as a blood thinner for those patients who are suffering from diseases that involve the thickening of the blood.

There are a lot of anticoagulants available today. First, the very common, aspirin. Next are serotonin uptake inhibitors which are Prozac and Paxil. Heparin is also considered to be an anticoagulant which is the most common anticoagulant that is used. Also, some Filipinos believe that Garlic and Ginkgo act as an anticoagulant, and lastly, herbal supplements that have warfarin. It was also proved that there are a lot of herbal plants that have anticoagulant activity, one of the things that were mentioned are *Allium sativum*, *Cucurma longa*, *Ananas comosus*, and *Lycopersicum esculentum* also pineapples, sunflower seeds and, many more.[8]

Many restrictions and harmful effects are related to the use of anticoagulants (heparin, warfarin). Bleeding is the most incurable problem associated with this treatment.[8] Increased bruising, having red or pink-colored urine, purple toes, and having more blood in a normal menstrual cycle are some of the side effects of taking an anticoagulant.[9]

In today's time, medicinal plants are widely used and common already. According to Fritzgerald (2020), medicinal plants have become the resource of people and are also considered the same as primary health care.[9] Almost 80% who live in developed countries are said to be depending on the practice of traditional medicine.[10] A report from the World Health Organization (WHO) comes out with a percentage of 80% of the global population that tends to rely on traditional medicines. Each medicinal plant has unique characteristics that help people to recover.

Coagulation is made up of a collection of zymogens that can be converted to active enzymes by minimal proteolysis, resulting in the formation of thrombin, which then transforms fibrinogen into fibrin. Thrombin is a pivotal enzyme in the coagulation pathways since it is responsible for the feedback activation of other coagulation factors. Sulphated macromolecules' anticoagulant and antithrombotic properties are among the most researched. Heparin, a glycosaminoglycan anticoagulant, is an effective therapeutic agent for thrombosis prevention and treatment; Dermatan sulfate (DS) is also anticoagulant but has a lower potency than heparin. Since flavonoids have free-radical scavenging activity, antioxidant properties, and inhibitory effects on platelets and leukocytes, they have been shown to affect a wide range of enzymes, making them of potential interest in the production of blood inhibitors and vessel wall interactions. Furthermore, flavonoids have recently been shown to inhibit platelet adhesion, aggregation, and secretion.[11]

Sulfate flavonoid: The polyphenols that have received the most attention are flavonoids. The nucleus of aurones, flavanonols, isoflavones, flavones, flavonols, and anthocyanins is 2-phenyl benzyl-pyrone, with great structural variation resulting in a variety of flavonoid forms, including aurones, flavanonols, isoflavones, flavones, flavonols, and anthocyanins.Flavonoids are known for a wide range of biological activities, and several studies have shown that sulfated flavonoids have pharmacological effects, including anticoagulant, anti-inflammatory, and antitumor properties.

Coumarin: The compounds are a form of lactone made up of a benzene ring fused to an α-pyrone ring, and they have a conjugated system with a lot of electrons and good charge-transport properties. Coumarin is derived from the French word coumarou, which refers to the Tonka bean seeds of Dipteryx odorata (Coumarouna odorata) (Fabaceae/Leguminosae), which was one of the first natural products to be isolated in 1820. Coumarin is an anticoagulant extracted from many plants. Coumarin functions by inhibiting calcium production in the blood coagulation cascade. Since phenolic coumarins have antithrombotic and thrombolytic activity, the antithrombotic activity of the test plant extract may be due to the phenolic coumarins, and the marked increase in prothrombin time and active partial thromboplastin time may be due to phenolic compounds interfering with calcium's procoagulant action.[12]

Triterpenoid Saponin: Triterpenoids saponin causes hemolysis of red blood cells (RBCs) forming a persistent froth if shaken with water, and it is also water and alcohol soluble. Saponin is a naturally occurring bioorganic compound that is found in particular abundance in the plant kingdom. Structurally, these compounds have one or more hydrophilic glycoside sugar moieties

fused with lipophilic triterpene molecules. These compounds form a foundation for the development of modern medicine or drugs.

Asteraceae Family

Specifically the family of Asteraceae which is considered to be the largest family of flowering plants. These are composed of Daisy (*Bellis perennis*), sunflower, or composite family. It was also stated by Native plants (2018) that Asteraceae is mostly composed of properties that help a lot in terms of anticoagulation that will benefit patients that are suffering from coronary diseases or diseases that involve clotting of blood.[13]

Objectives

This systematic review generally aims to provide an overview of the anticoagulant activity of some medicinal plants under the family of Asteraceae. Specifically, this review aims to review the phytochemical constituents of different Asteraceae plant extracts affecting coagulation and platelet inhibition.[14]

MATERIALS AND METHODS

Figure 1 above shows the detailed flow diagram guideline to be followed by the researchers in gathering data for the review. This is the system used to collect unbiased data by comprehensively searching to find all relevant studies. This system collates all that is known on the topic and identifies the basis of that knowledge and principle behind the mechanism of anticoagulation of each medicinal plant in the Asteraceae Family. It would start with formulating (1) Research questions, (2) Preliminary search, (3) Search Strategy, (4) Search Databases, which were separated by two-level filters that have different inclusion and exclusion criteria. After that is the (5) Manual search of the studies (e.g. reports on the studies and contacting the authors for access in the paper, then (7) Data Checking, and (8) Manuscript writing.

Research question and objectives

The gathering of the articles for the mini-reviews started by creating a question regarding the chosen topic. The research questions are formulated in PICO and SPIDER format. The researchers recommend a combined approach of using either one or both the SPIDER and PICO tools to retrieve a comprehensive search depending on time and resource limitations. When we applied this to our assumed research topic, being of qualitative nature, the use of the SPIDER approach is more valid. The researchers made sure that research questions are clear, logical, and relevant to the study.

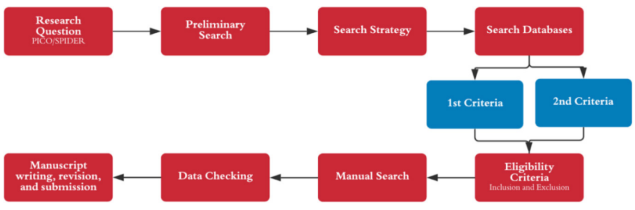

Figure 1: Detailed Flow Diagram Guideline of the Systematic Review.

Preliminary Search and Idea Validation

This systematic review was carried out based on the search of the keywords of interest. The keywords used were "Asteraceae" and "Anticoagulant" in reputable databases such as Google Scholar, Web of Sciences, PubMed, and ScienceDirect. The researchers begin with screening the titles of each study as well as their abstracts considering the eligibility criteria set. After the removal of studies of irrelevant studies, the full text of the remaining studies was manually checked to determine their relevance.

Search strategy

Eligibility criteria: Inclusion and exclusion

The inclusion and exclusion criteria were based on SPIDER (Sample, the phenomenon of Interest, Design, Evaluation, Research type) and PICO (Participant, Intervention, Control, and Outcomes (PICO) search strategy as well as qualitative research questions in formulating the eligibility criteria (Table 1). The researchers conducted two-step filtration to identify relevant studies, ensure the validity of the proposed idea and avoid the probability of bias in this review.

We considered experimental studies that contain Asteraceae plants showing anticoagulant activity. The inclusion criteria were studies that had quantitative

Table 1: PICO table illustrating the inclusion criterion.

PICOS	Inclusion Criteria
Population	Asteraceae plant with anticoagulant activity
Intervention	Provide use of crude extraction of Asteraceae plant Must contain phytochemical analysis of the plant extract
Comparison	Data from the different plant on measuring the anticoagulant activity
Outcome	Chemical constituents that are proven to have anticoagulant properties
Study Design	Must include: - Descriptive papers - Quantitative study methods based on the clotting time (PT, aPTT)

results in the anticoagulant activity of the plant extract. Chemical constituents that are proven to have anticoagulant properties and experiments that used crude extracts are included in the review. There were also no restrictions on the blood type as long as it does have no discrepancy in the coagulation activity. Inclusions based on the methodology part were also formulated, studies that measure anticoagulant activity by Prothrombin time (PT) and Activated partial thromboplastin time (aPPT) are included as well as studies that contain a phytochemical analysis of the plant extracts. Published dates between 2006 to 2021, Full-text articles, and English language are included. The exclusion criteria were qualitative studies that do not have an evaluation of the anticoagulant activity of the plant extract. Studies that do not conduct experimentation using either *in vivo* and *in vitro* tests are excluded from the review. Blood samples with coagulation discrepancy, non-full text articles and resources, non-English language studies, and articles that were not relevant to the purpose of the study were excluded.

RESULTS

Anticoagulant properties of the Asteraceae family

In the 17 articles that were reviewed, there are 12 phytochemical constituents in total that the researchers extracted to the Asteraceae plant of their choice, some of the researchers have two or more chemical constituents that were tested together, thus making the sample population into *n*=35. Based on the data presented in Figure 2. Flavanoid widely present (*n*=10, 28.6%), Coumarin (*n*=6, 17.1%), Phenolic compound (*n*=3, 8.6%), Sulphated polysaccharides (*n*=3, 8.6%), Tannins (*n*=3, 8.6%), Diterpenes (*n*=2, 5.7%), Saponin (*n*=2, 5.7%), terpenoid (*n*=2, 5.7%), Alkaloids (*n*=1, 2.9%), Esters (*n*=1, 2.9%), Kaurene (*n*=1, 2.9%), Glycoside (*n*=1, 2.9%). This data shows that these metabolites that were extracted have anticoagulant properties that are present in the Asteraceae family. The diseases such as Cardiovascular, Thromboembolic, and Diabetes were found to be the common diseases of the mentioned continents. Based on the phytochemical testing the plants have chemical constituents like flavonoids, coumarin, and polysaccharide that are proven to perform anticoagulant and thrombolytic activity.

Methods to Assess the Anticoagulant Activity of the Asteraceae family

Most of the studies used water, methanol, and ethanol solution to measure the chemical constituents that inhibit blood coagulation, and based on the data given

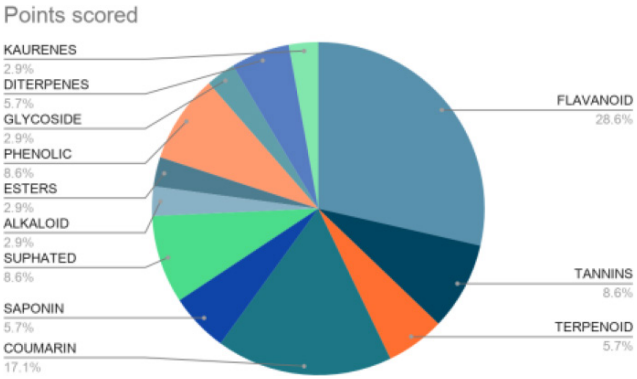

Figure 2: Chemical Constituents.

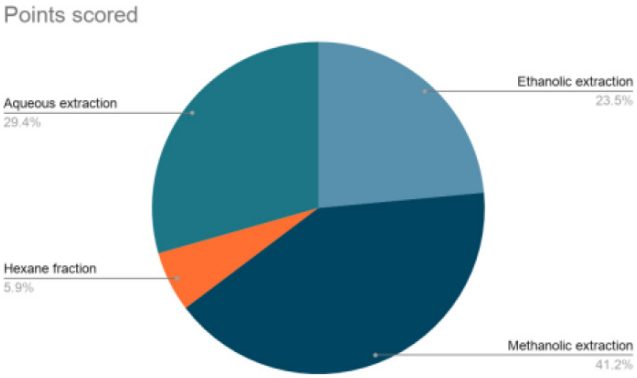

Figure 3: Methods of Extraction.

out of seventeen journals that we reviewed, Methanolic extraction is widely used (*n*=7, 41.2%), Aqueous Extraction (*n*=5, 29.4%), Ethanolic extraction (*n*=4, 23.5%), and Hexane Fraction (*n*=1, 5.9%), (Figure 3). Methanolic Extract are identified as the most effective solvent resulting in the highest concentration yield as well as the highest content of phenolic, flavonoid, alkaloid, and terpenoids and the coumarin derivative spots were more intense in the methanolic extract.

To measure the Intrinsic pathway two different tests were used and based on the data of the 17 journals that we reviewed, activated partial thromboplastin time (aPTT) is commonly used (*n*=13, 76.5%), Thrombin time (*n*=2, 11.8%), and studies that didn't use any test (*n*=2, 11.8%). The studies used *in vivo* and *in vivo* to monitor the intrinsic pathway. The result of the tests is prolonged aPTT and inhibition of the intrinsic coagulation pathway. It was determined that blood coagulation time was significantly decreased (Figure 4).

To measure the Extrinsic pathway two different tests were used and based on the data of the seventeen journals that we reviewed, the Prothrombin time is commonly used (*n*=14, 82.4%), Pure platelet plasma (*n*=1, 5.9%), and studies that didn't use any test (*n*=2, 11.8%). To

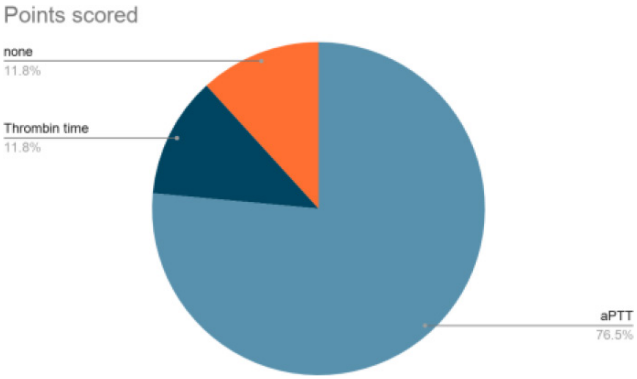

Figure 4: Evaluating the Intrinsic Pathway.

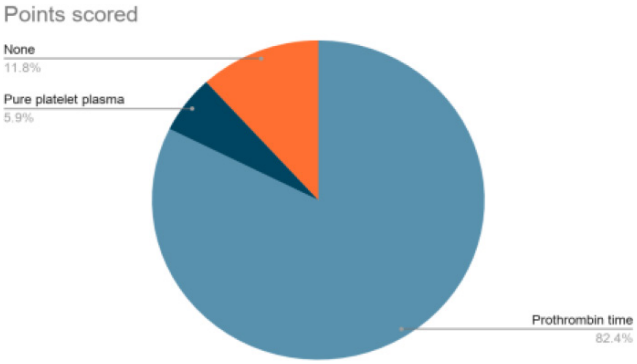

Figure 5: Evaluating the Extrinsic Pathway.

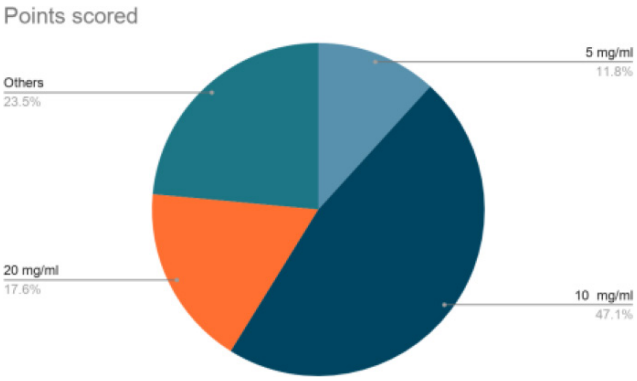

Figure 6: The concentration of Plant extract.

monitor the extrinsic pathway *in vitro* and *in vivo* were used in the studies. The result of the tests is prolonged prothrombin time by decreasing coagulation factors and inhibition of the extrinsic pathway of the coagulation cascade (Figure 5).

Data given shows the different concentrations of plant extract. All the fractions given, significantly prolonged the clotting time. Based on the data, in most cases of concentrations of 5 mg/mL (n=2, 11.8%) and 20 mg/ml (n=3, 17.6%), 10 mg/ml (n=47.1%) shows more effectiveness (Figure 6). The comparison effect of different fractions on the clotting time showed that the methanolic fraction is the most effective in inhibiting blood coagulation.

DISCUSSION

The chemical constituent of flavonoids, coumarin, and saponin was noted to have the most effect on anticoagulation activity. The presence of flavonoids, tannins, terpenoids, coumarins, and saponins has been suggested to play a crucial role in extract/fractions in hemostasis by reducing the time of plasma coagulation as well as blood clotting.[15] Coumarin-related compounds, phenolic compound flavonoids are known to exhibit antiaggregant, antiplatelet, and antimicrobial activities. While alkaloids, anthraquinones, and phlobatannins showed an absence of anticoagulation activity on reducing the time of plasma coagulation and blood clotting.[16] Studies of Asteraceae plants reveal different conclusions regarding relationships between the following chemical constituents. Although flavonoids, coumarin, and saponin proved to have effective anticoagulant activity, other compounds are still found less ineffective and require more in-depth analysis and study.[15,16]

A total of 14 plants were tested via *in vitro* analyses and used human blood as their sample assay. Different extraction methods were applied on each test, this includes water, aqueous, methanol, ethanolic, liquid-liquid extraction, and hexane fraction. Various controls are the saline solution, heparin sodium, EDTA, PBS, sodium citrate, ATS, NaOH 0.05M, saline, 1% Tween 80, and DMSO was also used. The Activated partial thromboplastin time and prothrombin time were also used to assess activity towards the intrinsic and extrinsic pathways.

A total of 5 plants were tested via *in vivo* analyses and used animals, specifically Wistar rats as their sample. Different extraction methods were used on the following test, this includes methanolic, aqueous, water, and liquid-liquid extraction. The control used for each test is plasma, nifedipine, phosphate-buffered saline, heparin sodium, 0.9% saline, and 0.5% ethanol. The activated partial thromboplastin time and prothrombin time were also used to assess the activity of the intrinsic and extrinsic pathways.

Unlike *in vitro* analyses, the *in vivo* used animals as their sample to assess the bleeding time with the correspondence of oral administration of drugs and plant extracts. Furthermore, methods of extraction play a crucial role in the experimentation, given that different methods can yield different results. The *in vivo* hemostatic activity test of *C. odorata* shows that

alcoholic extracts could stop bleeding better than the aqueous extract where 70% ethanol extract yielded the shortest bleeding time.[17] In the prothrombin time test of *Iphiona scabra* and *Jasonia montana,* aqueous-alcoholic extracts were used to orally administered to rats. Results show that the tested extracts induced a significant PT-prolonging effect after 4 hr and 24 hr.[18] While methanolic extraction was administered on both *Geoffroea spinosa* and *Crassocephalum crepidioides* plant species showing prolonged platelet aggregation, prothrombin time, and activated partial thromboplastin time. Meanwhile, in the liquid-liquid extraction of *Achillea santolina* an unclear *in vivo* effect was found in rats compared to *in vitro* analyses.[19] The antiplatelet effect of the *in vitro* analyses of *Achillea santolina* extracts was proved, but the modesty of the effects in the *in vivo* raises questions as to the clinical efficacy.[20] The result of the experiment shows that the method of extraction of ethanol, methanol, and liquid-liquid is effective in terms of preserving the anticoagulant properties of the plant extracts.

CONCLUSION

The medicinal properties of Asteraceae are recognized worldwide and have been evaluated showing the potential anticoagulant properties. As it is reviewed in this paper, plants under the Asteraceae family are mostly composed of properties that help a lot in terms of anticoagulation that will benefit patients that are suffering from coronary diseases or diseases that involve clotting of blood. Scientific data along with coagulometric test results support the paper that the anticoagulant activity is due to the inhibition of coagulation factors provided by the synergism between the various compounds present in different plants from the family Asteraceae such as coumarins, diterpenes, flavonoids, and phenylpropanoids. The researchers would like to recommend the future researchers try one specific type of plant coming from the Asteraceae family, specifically *Bellis perennis* to have accurate results about their anticoagulant properties. It would be also good if future researchers would explore more about the plant in terms of anticoagulant properties, antimicrobial properties, or anti-inflammatory properties.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

aPTT: Activated partial thromboplastin; **PT:** Prothrombin time; **DS:** Dermatan sulphate; **RBC:** Red blood cells; **SPIDER:** Sample, Phenomenon of Interest, Design, Evaluation, Research type); **PICO:** Participant, Intervention, Control, and Outcomes; **EDTA:** Ethylenediammine tetraacetic acid; **PBS:** Phosphate buffer solution; **ATS:** quercetin 3-acetyl-7,3,4'-trisulphate; **NaOH:** sodium hydroxide; **DMSO:** Dimethylsulfoxide

SUMMARY

The members of Asteraceae family possess rich reservoir of important phytochemicals such as flavonoids, alkaloids, and polyphenols. Hence, these plants are seen as potential sources of compounds of anticoagulant activities. In this systematic review, the anticoagulant properties of Asteraceae family was surveyed. Using SPIDER and PICO methods, 17 articles were included. Scientific data along with coagulometric test results support the paper that the anticoagulant activity is due to the inhibition of coagulation factors provided by the synergism between the various compounds present in different plants from the family Asteraceae such as coumarins, diterpenes, flavonoids, and phenylpropanoids.

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