Review Article

Potential use of plants and their extracts in the treatment of coagulation disorders in COVID-19 disease: a narrative review

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Abstract: Coronavirus disease, i.e., COVID-19, is caused by the virus called "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)". Infection induces predominantly respiratory illness but is also associated with coagulation disorders which play an important role in the pathogenesis, clinical manifestations, and outcome of the disease. The treatment of hemostasis disorders of COVID-19 patients is a difficult problem to solve. For example, heparin is quite effective drug in reducing mortality in severe COVID-19 forms but not able to prevent venous and arterial thromboembolic complications. Moreover, anticoagulant therapy with heparin is associated with several adverse reactions, such as thrombocytopenia, osteoporosis, hypoaldosteronism and hypersensitivity reactions. New alternative anticoagulant molecules can be obtained from plants which are rich in polyphenols and flavonoids. These compounds, besides being potent antioxidants, also possess anti-inflammatory effect and, because able to inhibit the activity of many enzymes, including serine proteases, also anticoagulant properties. The purpose of this narrative review is to provide an overview of current literature data on coagulation disorders associated with COVID-19 disease and of the anticoagulant activity of plants and their extracts in order to evaluate their possible clinical application as alternative sources of novel molecules with anticoagulant and antithrombotic activity for the treatment of coagulation disorders in patients with COVID-19.

Keywords: COVID-19 coagulopathy; anticoagulants; low molecular weight heparin (LMWH); plants; natural extracts

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Introduction

Coronavirus disease, i.e., COVID-19, is caused by the virus called "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)". The infection mainly induces respiratory diseases but is also associated with coagulation alterations that significantly affect both the clinical manifestations and the outcome of the illness.

Coagulation disorders, developed by about 60–70% of the hospitalized patients, involve venous thrombosis (VT), hypercoagulation, thrombocytopenia, and disseminated intravascular coagulation (DIC) (1,2). These coagulation disorders have different clinical manifestations than the classic DIC syndrome. They are defined as COVID-associated coagulopathies (1-3) and include: an increase in both activated partial thromboplastin time (APTT) and prothrombin time (PT), an increase in the thrombin-antithrombin (TAT) complex, D-dimer and fibrin degradation products (FDP), and the decrease of antithrombin (AT) in plasma samples from hospitalized patients (4).

The treatment of hemostasis disorders of COVID-19 patients is a difficult problem to solve. For example, heparin, mainly low molecular weight heparin (LMWH), is quite effective drug in reducing mortality in severe

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COVID-19 patients but not able to prevent venous and arterial thromboembolic complications (4,5). Moreover, anticoagulant therapy with heparin is associated with several adverse reactions, such as thrombocytopenia, osteoporosis, hypoaldosteronism and hypersensitivity reactions (6). For this reason, it is necessary to set up therapeutic schemes that envisage the use and optimal dosage of effective anticoagulant and antithrombotic drugs, for both the prevention and treatment of coagulation disorders in COVID-19 patients (7,8).

New alternative anticoagulant molecules can be obtained from plants because they are rich in many phytochemical compounds with different bioactivities. It has been widely demonstrated that plant extracts characterized by having good antioxidant properties also have anticoagulant effects (9). The classes of compounds responsible for this anticoagulant activity seems to be those of polyphenols and flavonoids that show inhibitory capacity towards many enzymes including several serine-proteases involved in the coagulation cascade (10-12). The correlation between the anticoagulant/antithrombotic effect of natural extracts and their polyphenol and flavonoids content has also been further demonstrated by many epidemiological studies (13).

The purpose of this narrative review is to provide an overview of current literature data on coagulation disorders associated with COVID-19 disease and the anticoagulant activity of natural extracts in order to evaluate their possible clinical application as alternative sources of novel molecules with anticoagulant and antithrombotic activity for the treatment of coagulation disorders in patients with COVID-19. I present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/lcm-21-23).

Research method

The literature published was collected from databases including Medline, PubMed, Elsevier, Web of Science, Google Scholar databases using English language as a restriction. The key words used were: "COVID-19 disease" or "COVID-19 associate coagulopathy" or "COVID-19 deep vein thrombosis" or "COVID-19 venous thromboembolism" or "COVID-19 anticoagulant treatments" or "natural extracts anticoagulant activity" or "plants anticoagulant activity" or "polyphenols, flavonoids and polyphenols/flavonoids anticoagulants" or "LMWH and COVID-19" or blood-coagulation pathways" or "complement activation and COVID-19" or "NETs and COVID-19". Reference lists of the most relevant review articles were also screened for additional studies not captured in initial literature search.

Inclusion and exclusion criteria

The search for this review was solely performed on English language, up to 2021, reporting clinical, and pharmacological data. In order to grant reliability, only publications on peer-reviewed journals were chosen. Moreover, number of citations and impact factor of the journals were other methods used to decide whether a study met the inclusion criteria of the review.

Blood coagulation pathways

Blood coagulation is a physiological process which main role is prevention of bleeding and blood loss from injured vessels. In healthy individuals, blood circulates in liquid form, but as a result of vascular damage it quickly gels to form a clot in order to prevent bleeding.Two main pathways for blood clotting have been described: the extrinsic or tissue factor (TF) pathway and the intrinsic or contact pathway (14). Both these pathways then converge in the common pathway which culminates with the formation of fibrin by fibrinogen cleavage thank to thrombin action.

The extrinsic pathway is activated as a consequence of the binding between the protein TF, present on the membrane of the cells surrounding the blood vessels, and the factor VII or VIIa in plasma. Once formed, the TF-VIIa complex can convert both factor IX to IXa and factor X to Xa (15).

The intrinsic or contact pathway is activated when factor XII (i.e., Hageman factor) contacts and binds an artificial or negatively charged surface. In this case there is a local increase in the concentration of factor XII which results in its self-activation at XIIa. Factor XIIa catalyzes both kallikrein formation by conversion from prekallikrein and activation of factor XI (16). At the same time the high molecular weight kininogen (HMWK) is cleaved. All these reactions lead to the activation of factor IX (17) which, together with factor VIIIa, calcium and phospholipids, forms the complex called "tenase" able of activating factor X. In plasma, factor VIII is bound to von factor Willebrand (vWF) which prevents its activation by plasma serine proteases. Due to the binding of vWF to platelets attached to the surface of the damaged

endothelium, activation of factor VIII and dissociation of vWF is promoted (18). Factor VIII can also be activated by thrombin directly and this process cannot be blocked by vWF (19). The last step of the coagulation cascade, culminating with the production of active thrombin, is the formation of the prothrombinase complex formed by factor Xa linked to factor Va, its non-enzymatic cofactor, calcium and the surface of a phospholipid membrane. In the presence of both anionic phospholipids and thrombin, factor V is activated (20). Even factor Xa alone can catalyze the conversion of prothrombin into thrombin by a very slow reaction that can be accelerated by adding factor Va and by binding the complex to the phospholipid surface of activated platelets or monocytes (21). The tenase complex activates conversion of prothrombin into thrombin, the serine protease able of converting fibrinogen into fibrin and activating platelets, factors V, VIII and IX, protein C inhibitors and fibrinolysis inhibitor (22,23).

Finally, in the common pathway of coagulation, soluble fibrinogen is converted into a network of insoluble fibrin, which closes the lesion site of the vascular endothelium, preventing blood bleeding. protecting the damaged tissue and promoting wound healing.

Platelets, or thrombocytes, are small anucleated cells that originate in the bone marrow from megakaryocytes. Platelets play a very important role in coagulation as they adhere and aggregate rapidly at the level of vascular lesions, forming the platelet plug, and their membrane, being rich in negatively charged phosphatidylserine, favors the formation of thrombin, thus amplifying the blood coagulation cascade (24,25). Moreover, the activation of platelets, a process that alters the permeability of the membrane and allows the entry of calcium, the release of chemotactic substances that attract the coagulation factors to the surface and the release of factor V and acid phospholipids, further contributes to the amplification of the coagulation process. Besides their role in platelet plug formation, platelets provide the surface on which the tenase and prothrombinase complexes form (26-28). So, platelet adhesion, aggregation and activation play a central role in different stages of the coagulation cascade and are also actively involved in cell-based thrombin generation, which greatly amplifies the blood coagulation cascade (29-33).

Numerous regulatory mechanisms exist to prevent general activation of the blood coagulation system as for example substances that oppose blood clotting, preventing it or simply delaying it. These substances are called anticoagulants. One of the most important is heparin, found mainly in the liver and lungs, which acts when there is excessive coagulation, to prevent pathological situations such as thrombosis. AT III is a small glycoprotein produced by the liver that deactivates several serine-proteases involved in coagulation cascade. Protein C is the major physiological anticoagulant. Its synthesis occurs in the liver and is vitamin K-dependent. It is activated by thrombin in active protein C. The active form of protein C inactivates factor V and factor VIII of coagulation through a proteolysis mechanism. Protein S is another amino acid vitamin K-dependent protein and is mainly synthesized by the liver and endothelial cells. It acts as a cofactor of protein C and enhances its activity.

Pathogenesis of coagulation disorder associated to COVID-19 disease

The SARS-CoV-2 virus causes severe acute respiratory syndrome and systemic disorder which induces a prothrombotic state characterized by VT, hypercoagulation, thrombocytopenia, and DIC (1,2). The presence of coagulopathies in COVID-19 patients is associated with the alteration of many laboratory coagulation parameters among which the most relevant are the decrease of platelet number and fibrinogen level, increase of D-dimer concentration and PT prolongation (34,35). In any case, the virus itself does not have intrinsic procoagulant effects; rather, coagulopathy is the result of the profound COVID-19 inflammatory response and endothelial activation/damage and is likely due to the interdependence between the inflammatory and hemostatic systems (36-39).

Prothrombotic state is related to the infection mechanism of the SARS-CoV-2 virus and there are three pathways that contribute to its establishment. The first concerns the binding between angiotensin converting enzyme 2 (ACE-2) receptors on endothelial cells and the virus. This binding triggers a localized inflammatory reaction accompanied by endothelial activation, tissue damage and altered release of cytokines such as tumor necrosis factor and interleukins-1, 2 and 6 (40). In particular, the decrease in the level of ACE-2 following the penetration of the virus into the cells, causes the interruption of the transformation of angiotensin-II (AngII) into angiotensin, a peptide with anti-inflammatory and vasodilating activity (41). Hence, plasma levels of AngII increase as well as its effects: vasoconstriction, activation of platelet and endothelial cells and release of

pro-inflammatory cytokines (41).

The second pathway involves the neutrophil extracellular traps (NETs), networks of extracellular fibers, primarily composed of DNA from neutrophils, which kill pathogens and promote vessel occlusion by providing a scaffold for platelets, red blood cells, and procoagulant molecules. Moreover, NETs components enhance coagulation through both the intrinsic and extrinsic pathways resulting in enhanced thrombin generation (42,43). The overactivation of neutrophils can promote the formation of immune-thrombosis and even cause DIC, which damages microcirculation. The interaction of NETs with platelets, complement, and endothelium mediates the formation of immune-thrombosis. It has been demonstrated that the formation of NETs is directly correlated, in various conditions, both at systemic and local level, not only to inflammation but also to coagulation and thrombosis (44,45). Therefore, despite the positive effect of NETs in defending the host organism from pathogens, their overexpression, as happens in the presence of COVID-19 infection, can trigger a series of cascade inflammatory reactions able of damaging the surrounding tissues, even in the absence of immune cell infiltration (46).

The third pathway concerns the dysregulation of complement activation. The complement system is one of the most important defense mechanisms of the immune system. It consists of a set of proteins, synthesized by the liver, present in the serum as inactive enzymatic precursors (zymogens) and membrane proteins that undergo cascade activation. The role of the complement system is the elimination of the pathogen, in direct form, through the lysis of the microorganism, or indirectly, through the phagocytosis of foreign agents, the activation of inflammation (with the attraction of different cells and molecules) and elimination of the antigen-antibody immune complexes (47). The complement and coagulation systems, which share multiple factors, are closely interconnected, in balance with each other and involved in the pathophysiology of various diseases, including COVID-19 (48). To support this, there are experimental data demonstrating the procoagulant effect of the complement system in the presence of COVID-19. This effect appears to be directly mediated by mannose-associated serine protease-2 (MASP-2), a critical component able to activate thrombin resulting in fibrin formation (48). Furthermore, the components of the complement, indirectly, can induce alterations at the level of the endothelium able to modulate the coagulation cascade. Finally, complement is also actively involved in platelet aggregation, an effect closely related to the corpuscular phase of coagulation. The coagulation system can, in turn, activate complement through the activation of factor XIIa which can activate the complement complex C1 (49). Thus, there is a clear reciprocal interaction between coagulation and complement, and the synergistic activation of these two systems in COVID-19 patients can increase the extent of coagulopathy. For this reason, it seems plausible that the severe symptoms of COVID-19 may be due to the combined effects of complement activation, overproduction of NETs, endothelial damage and hypercoagulability (46).

Anticoagulant prophylaxis and treatment in the management of COVID-19 patients

LMWH is an anticoagulant drug obtained by enzymatic digestion or chemical depolymerization of unfractionated heparin (UFH) (50). LMWH, having a shorter polymer chain than UFH, has a longer half-life and more predictable bioactivity. LMWH inhibits the final common pathway of the coagulation cascade, which is the conversion of fibrinogen to fibrin by thrombin. LMWH works by activating AT III which binds and inhibits factor Xa, preventing the activation of the final coagulation pathway, i.e., the transformation of prothrombin into thrombin and the conversion of fibrinogen into fibrin (50). LMWH is used in clinical practice for the prophylaxis and treatment of various pathologies such as venous thromboembolic disease (VTE), deep vein thrombosis (DVT), pulmonary embolism (PE), in the prevention of coagulation in extracorporeal circuits, in unstable angina. Anticoagulant therapy with LMWH is associated with several adverse reactions, the most common of which is bleeding. More rarely, other adverse effects such as thrombocytopenia, osteoporosis related to increased spontaneous fractures, hypoaldosteronism and hypersensitivity reactions may occur (50). Treatment of COVID-19 patients with LMWH is widely accepted as standard anticoagulant therapy (51) and is preferred over UFH due to the advantages of LMWH, such as reduced bleeding risk, good predictability, dose-dependent plasma levels, and half-lives longer (52,53). Many retrospective studies conducted on the effects of heparin, mainly LMWH, confirm anticoagulant treatment with heparins to be beneficial in COVID-19 (54). In a retrospective study performed in China anticoagulant therapy mainly

with LMWH appeared to be associated with better prognosis in severe COVID-19 patients meeting sepsis-induced coagulopathy (SIC) criteria or with markedly elevated D-dimer (5). In part, this beneficial effect of LMWH could be explained also by its non-anticoagulant properties which could be play an important role in the treatment of COVID-19 patients (55). The anti-coagulant mechanisms of LMWH include: inhibition of heparanase activity, responsible for endothelial leakage; neutralization of chemokines, and cytokines; interference with leukocyte trafficking; reducing viral cellular entry; neutralization of extracellular cytotoxic histones (55). Therapeutic anticoagulant treatment with LMWH could increase the survival rate of COVID-19 patients by interfering with various pathological processes.

Anticoagulant and antithrombotic activity of natural plants and their extracts for potential use in COVID-19 patients

Plants, thanks to their numerous beneficial properties, have been widely used since ancient times for therapeutic or preventive purposes. Nowadays there is a growing interest in the study of active ingredients obtained from plant species because, thanks to their specific bioactivity, they can be used for specific purposes in humans (56). The bioactivity of plant extracts and their application targets essentially depend on the type and quantity of classes of chemical compounds present (57).

Polyphenols and flavonoids, compounds found in large quantities in plants and in their extracts, besides being potent antioxidants, also possess anti-inflammatory effect and, because able to inhibit the activity of many enzymes, including serine proteases, also anticoagulant properties (58,59). Based on described properties, polyphenols, flavonoids and polyphenol/flavonoids-rich extracts could be very helpful with both prevention and treatment of thromboembolic complications associated with multiple failures of hemostasis as well as in COVID-19 coagulopathy, because the therapeutic drugs currently available, such as LMWH, do not offer the same multiple effects (anticoagulants, antioxidants and anti-inflammatory) (60). So, plants and their extracts may represent alternative sources of anticoagulant molecules and there is scientific evidence that the introduction of food anticoagulants with the diet can help reduce the risk of thromboembolic diseases (61,62). Below are reported some plants whose extracts have been shown to have *in vitro* anticoagulant activity. Moreover, also the anticoagulant properties of isolated compounds were described in order to correlated the extract phytochemical composition with its ability to interfere with blood coagulation.

Careya arborea Roxb (63) is a deciduous tree belonging to the *Lecythidaceae* family, native to Afghanistan, Andaman Islands, Assam, Bangladesh, Cambodia, India, Laos, Malaysia, Myanmar, Nepal, Thailand. It is commonly known as Guava Selvatica, Ceylon Oak, Patana Oak. It has leaves that take on a red color in cold season, and yellow or white flowers that turn into large green berries (64). The methanolic extract obtained from *C. arboreaa*, rich in phenolic compounds with a good antioxidant property, shows anticoagulant activity comparable to that of warfarin, an anticoagulant commonly used to treat blood clots such as DVT and PE (65), by increasing APTT, PT and thrombin time (TT) (64). This anticoagulant activity is correlated with the high level of gallic acid, 3,4-dihydroxybenzoic acid, quercetin 3-O-glucopyranoside, kaempferol 3-oglucopyranoside and quercetin 3-O-(6-O-glucopyranosyl)-glucopyranoside (66).

Rosmarinus officinalis (family *Lamiaceae*) (67) is one of the oldest Mediterranean evergreen shrubs with aromatic needle-like leaves. The upper part of the leaves is dark-green and the lower part is silvery, with a margin that tends to rise. The flowers are small, blue-purple; the fruits are tetrachenes, brown when ripe. *R. officinalisis*, nowadays cultivated all over the world, is a rich source of antioxidants and anti-inflammatory compounds, able to improve strengthen the immune system and improve blood circulation. Rosemary, the popular name of *R. officinalis*, is considered a cognitive stimulant and can help improve memory performance and quality. It is also known to increase alertness, intelligence, and focus. For such effects it is used in traditional and complementary alternative medicine in many countries. Recently, it has been shown that the ethanolic extract of *R. officinalis* has an anticoagulant effect which is expressed by prolongation of the TT. These data suggest that the extract inhibits the activity of thrombin preventing its action on fibrinogen and the consequent formation of fibrin (68). Since coagulation and inflammation are interrelated processes that can influence each other (69), based on experimental studies reported in the literature (70), it can be hypothesized that the inhibitory modulation of coagulation by the extracts may be due to the same mediators of anti-inflammatory activity, i.e., triterpenes, ursolic acid and its isomer oleanolic

acid, betulinic acid, carnosol, and micromeric acid (70,71). Triterpenes and their derivates, possess not only antioxidant and anti-inflammatory properties, but may also display anticoagulant activity in terms of thrombin inactivation (72). Betulinic acid also shows antithrombotic, antiplatelet aggregations and anticoagulants potential. The isolated compound, in fact, is able to attenuate platelets aggregation induced by thrombin, and to inhibit AT activity in a dose dependent manner (73). Carnosol has a potent antiplatelet activity *in vitro*. In platelet aggregation study, carnosol inhibited washed rabbit platelets aggregation induced by thrombin, collagen, arachidonic acid and U46619 in a dose-dependent manner (74).

The family *Thymus* (75) includes about 350 species of aromatic perennial herbaceous plants (commonly known as Thyme) native to the western Mediterranean regions that grow spontaneously above all in arid, stony and sunny soils both in the mountains and in the plains, although more frequently present near the sea. They are plants with numerous virtues and benefits. Among the various known species, *Thymus atlanticus* and *Thymus zygis* are those used in folk medicine thanks to their anti-inflammatory properties, in the form of infusions and decoctions for the treatment of respiratory symptoms, such as pertussis and bronchitis, of rheumatism (76). The aqueous extracts of *Thymus atlanticus* and *Thymus zygis*, rich in polyphenol and flavonoid compounds such as caffeic acid, rosmarinic acid, quercetin, rutin, hyperoside and luteolin-7-O-glucoside show *in vitro* strong anticoagulant activity as demonstrated by inhibition of plasma clot formation both in APTT and TT test (77-79). Study performed on isolated compounds, demonstrated that caffeic acid significantly inhibits thrombin-induced platelet aggregation, fibrinogen-binding to integrin $\alpha_{IIb}\beta_3$, platelet-mediated clot retraction, and activates cyclic adenosine monophosphate (cAMP) generation. These findings suggest that caffeic acid might be an excellent starting point for the development of novel therapeutic agents for thrombotic disorders (80).

In vitro, rutin inhibits in a dose-dependent manner the platelet activating factor responsible of intra-platelet free calcium concentration, decreasing the degree of platelets aggregation in rabbits (81).

The results of *in vitro* and *ex vivo* coagulation studies show that APTT was significantly prolonged and the PT was delayed also by quercetin (82). Moreover, bioinformatic analyses reported by Bijak *et al.* (83) revealed that quercetin together with procyanidin B2, cyanidin and silybin has inhibitory effect on FXa activity, a novel target for modern anticoagulant therapy. Bioinformatic analyses revealed that procyanidin B2, cyanidin, quercetin and silybin bind in the S1–S4 pockets located in vicinity of the FXa active site and block access of substrates to Ser195. These data demonstrate that flavonoids might be potential structural bases for design of new nature-based, safe, orally bioavailable direct FXa inhibitors (83).

Viola yedoensis Makino is commonly used in Chinese herbal medicine for its anti-*Helicobacter pylori* and anti-HIV activity (84). Dimeresculetin, a dicoumarin isolated from *Viola yedoensis* Makino, shows anticoagulant activity being able to prolong APTT, PT and TT (85).

The family *Asteracea*, alternatively named *Composita*, consists of over 32,000 known species of flowering plants in over 1,900 genera within the order *Asterales*. Plants belonging to *Asteraceae* family have good antioxidant and anticoagulant activity. It has been shown that macromolecular polysaccharides conjugated with polyphenols, isolated from herbaceous plants of the *Asteraceae* family, plants frequently used in Polish folk medicine, have a high antioxidant power and protect platelets from oxidative damage induced by biological oxidants (86). The anticoagulant activity evaluation performed on extracts obtained from different plants belonging to *Asteraceae* and *Rosaceae* families, demonstrated that phytochemicals isolated from *Fragaria vesca* (*Rosaceae*) and *Echinacea purpurea* (*Asteraceae*) are able to prolong both PT and APTT (87). The observed anticoagulant activity appears to be due to the high content of hexuronic acids and phenolic glycoconjugates, compounds in which the extracts are rich. Thanks to a study performed by Pawlaczyk *et al.* (88) it was demonstrated that the anticoagulant activity showed by *Erigeron canadensis* L. extracts was due to the inhibitory effect of AT and heparin cofactor II against thrombin and FXa, of polyphenolic-polysaccharide (PP) complexes isolated from the plant. The polysaccharide part, the 32% of the total mass, contains mainly hexuronic acids, and much smaller amounts of glucose, arabinose, galactose, as well as some traces of mannose, xylose and rhamnose. Polyphenolic part is rich in hydroxylic rests and in carboxylic groups, free and esterified (88). Therefore, plants belonging to the *Asteraceae* family have been shown to possess both anticoagulant and antioxidant activity and represent a source of PP complexes with heparin activity potentially suitable for the prevention and/or treatment of thromboembolic complications even in COVID-19 patients.

EuRP-61 is a serine protease isolated from the plant

latex of *Euphorbia resinifera* and, thanks to its anticoagulant activity, may be a potential agent for the treatment of thrombosis (89). This serine-protease hydrolyzes all chains of human fibrin clots and it is not affected by human blood circulating inhibitors such as α2-macroglobulin and AT III. EuRP-61 may influence all the three pathways of human coagulation cascade, i.e., extrinsic, intrinsic and common, and exerts its activity by prolonging both PT and APTT. Moreover, the enzyme inhibits platelet aggregation via the ADP-receptor pathway (89).

Cistanche, *Orobanche*, and *Phelipanche* spp, holoparasitic plants of the *Orobanchaceae*, are rich in phenylpropanoid glycosides (PPGs) which possess a wide spectrum of activities, such as antimicrobial, anti-inflammatory, antioxidant, and anticoagulant (90). Studies regarding the bioactivity of European broomrapes (*O. caryophyllacea*, *P. arenaria*, *P. ramosa*) and single isolated PPGs, demonstrated antioxidant and anticoagulant properties in terms of prolongation of APTT, PT and TT. The anticoagulant potential of these compounds, as well as their antioxidant activity, is related to their chemical structure, especially to the presence of acyl and catechol moieties. Thanks to these properties, selected PPGs, i.e., tubuloside A, poliumoside and 3-O-methylpoliumoside, exhibit the potential for treating cardiovascular diseases associated with oxidative stress (90).

Licania rigida Benth crude leaf extract (CELR) and ethyl acetate fraction (AFLR) demonstrated to possess *in vitro* anticoagulant activity (91). In particular, the extracts are able to prolong both APTT and PT at a concentration of 50 mg/mL and possess anti-factor Xa and anti-factor IIa activity. However, only AFLR inhibits 100% of the thrombin at a concentration of 100 mg/mL (91). The anticoagulant effects of the *L. rigida* extract may occur because of synergistic actions of polyphenols and their interactions with biomolecules which can interfere with biological activity. Gallic acid, catechin, chlorogenic acid, caffeic acid, epicatechin, ellagic acid, rutin, quercitrin, quercetin, kaempferol and kaempferol glycoside are the major constituents of *L. rigida* extracts which may be involved in their anticoagulant properties (92). This implies that a plant extract may provide a favorable response compared to the use of a single compound (93).

Extracts obtained with different solvents, i.e., petroleum ether, ethyl acetate, chloroform and methanol, from *Fumaria officinalis* L., a plant widely used in Tunisia, demonstrated high phenolics and flavonoids contents and anticoagulant activity (94). In particular, methanolic extract showed the highest total phenolic and flavonoids contents and the best antioxidant and anticoagulant properties in terms of prolongation of both APTT and PT (94).

Two fractions, with different molecular weights, of glycoconjugates extracted from *Genipa americana* leaves (PE-Ga) composed mainly by arabinose, galactose and uronic acid, are able to prolong clotting time-APTT and to inhibit by 48% the ADP-induced platelet aggregation (95). Moreover, *in vivo*, these glycoconjugates inhibit venous thrombus formation and increase bleeding time. So, the arabinogalactan-rich glycoconjugate of *G. americana* leaves, containing uronic acid, present antiplatelet, anticoagulant (intrinsic/common pathway) and antithrombotic effects, with low hemorrhagic risk (95).

PP conjugates obtained from *Pseuderanthemum palatiferum* (Nees) Radlk. leaves contained carbohydrate, phenolic, and protein constituents. Seven mono-sugars were found: arabinose, fucose, galactose, glucose, mannose, rhamnose, and xylose. PP conjugates exhibit anticoagulant activity by prolonging both APTT and PT (96).

In *Table 1* is reported a brief summary of all the plants cited in the text, classes of metabolites present in their extracts and their anticoagulant activity.

Conclusions

All the plants reported in this review are currently available as ingredients of commercial food supplements not intended for the prevention of thrombotic events but thanks to their anticoagulant effect, they can be used for the treatment of pathological processes associated with a greater thrombin generation as well as in COVID-19 patients. Moreover, they could be used in conjunction with anticoagulants currently administered in clinical practice to increase the efficacy of anticoagulant therapy after thrombotic events such as those related to covid SARS-CoV-2 infection. To do this, studies aimed at identifying the compounds and their exact mechanism of action in order to demonstrate their possible interaction with anticoagulant drugs of clinical use, as well as their adverse effects, are necessary. Until now, no clinical trials have been started regarding the use of antioxidants in anticoagulant therapy. Further research requires adequate clinical studies on the antioxidants present in natural extracts in the primary and secondary prevention of thromboembolic complications. However, there is no doubt that extracts obtained from plants could represent excellent candidates for the treatment of coagulation disorders related to COVID-19 disease.

Table 1 Summary of all the plants cited in the text, classes of metabolites present in their extracts and their anticoagulant activity

Plants	Classes of metabolites in the extracts	Anticoagulant activity of the extracts
Careya arborea (64-66)	Gallic acid, 3,4-dihydroxybenzoic acid, quercetin 3-O-glucopyranoside, kaempferol 3-Oglucopyranoside, quercetin 3-O-(6-O-glucopyranosyl)-glucopyranoside	*In vitro* prolongation of APTT, PT and TT
Rosmarinus officinalis (67-74)	Triterpenes, ursolic acid, oleanolic acid, betulinic acid, carnosol, micromeric acid	*In vitro* prolongation of TT
Thymus atlanticus, Thymus zygis (75-83)	Caffeic acid, rosmarinic acid, quercetin, rutin, hyperoside, luteolin-7-O-glucoside	*In vitro* prolongation of APTT and PT
Viola yedoensis (84,85)	Dimeresculetin	*In vitro* prolongation of APTT, PT and TT
Fragaria vesca, Echinacea purpurea, Erigeron canadensis (86-88)	Hexuronic acids and phenolic glycoconjugates	*In vitro* prolongation of APTT and PT
Euphorbia resinifera (89)	Serine protease EuRP-61	*In vitro* prolongation of APTT and PT and inhibition of platelet aggregation via the ADP-receptor pathway
Orobanche caryophyllacea, Phelipanche arenaria, Phelipanche ramose (90)	Phenylpropanoid glycosides: tubuloside A, poliumoside, 3-O-methylpoliumoside	*In vitro* prolongation of APTT, PT and TT
Licania rigida (91-93)	Gallic acid, catechin, chlorogenic acid, caffeic acid, epicatechin, ellagic acid, rutin, quercitrin, quercetin, kaempferol and kaempferol glycoside	*In vitro* prolongation of APTT and PT and anti-Xa and anti-IIa activity
Fumaria officinalis (94)	phenolics and flavonoids	*In vitro* prolongation of APTT and PT
Genipa americana (95)	Glycoconjugates composed mainly by arabinose, galactose and uronic acid	*In vitro* prolongation of APTT and inhibition of ADP-induced platelets aggregation; *in vivo* inhibition of venous thrombus formation and increasing of bleeding time
Pseuderanthemum palatiferum (96)	Polyphenolic-polysaccharide conjugates	*In vitro* prolongation of APTT and PT

APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time.

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