Peer Review File

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Reviewer comments
Reviewer A

The text has been revised in order to ensure good presentation and understanding of your work. Revision are reported in red color.

Comment 1: Line 36 (now line 34) – a final point is missing after "properties".
Reply 1: the full stop has been added.
Changes in the text: .

Comment 2: Line 65 (now line 63) – insert the reference about plants that present antioxidant and anticoagulant activities.
Reply 2: reference has been added.
Changes in the text: (9)

Comment 3: Line 77 (now lines 78-82) – normalize the key-words separation with "," or ";". Choose only one way to separate the terms.
Reply 3: the key-words separation has been normalized.
Changes in the text: or

Comment 4: Line 255 – please, abbreviate and correct the plant genus to C. arborea.
Reply 4: abbreviation and correction done.
Changes in the text: *C. arborea*

Comment 5: Line 257 (now line 253)– abbreviate the plant name.
Reply 5: abbreviation done.
Changes in the text: *R. officinalis*

Comment 6: References - please, normalize the reference list. Choose all first letters in upper or lower case.
Reply 6: reference list has been normalized.
Changes in the text: ref. 40 Liu Z, Xiao X, Wei X, et al. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. J Med Virol. 2020; 92:595-601. doi: 10.1002/jmv.25726;
ref. 48 Tomo S, Kumar KP, Roy D, et al. Complement activation and coagulopathy - an ominous duo in COVID19. Expert Rev Hematol. 2021; 14:155-73. doi: 10.1080/17474086.2021.1875813.
All other references have been normalized.

Comment 7: The title targets plant extracts and compounds about a disease, but more than a half of the entire written manuscript was dedicated to mechanisms of actions of relations immunologic responses of important relation diseases that affect the COVID-19 patient…..
Reply 7: the title targets at the role of plants and their extracts in the prevention of coagulopathies COVID-19 correlated. For this reason, part of the review is dedicated to the description of the coagulation cascade and the mechanism of the coagulation disorder due to COVID-19 infection. The

aim is to demonstrate that some anticoagulant activities shown by plants and their extracts can act at the level of coagulation and be involved in the prevention or treatment of coagulopathies related to COVID disease. If we do not know which step of the coagulation cascade is altered in COVID patients, we cannot hypothesize a treatment with plants or their extracts.
Furthermore, the objective of the review is to report the state of the art of knowledge of a potential contribution of plants and their extracts to the prevention of coagulation disorders in COVID patients.
As reported in the text lines 236-238 "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 (59,60)." Anyway, when identified, compounds involved in the anticoagulant activity of plants and extracts, if not reported in the precedent version of the manuscript, have been added as well as their bioactivity as isolated compounds

Changes in the text:

Lines 253-258: The methanolic extract obtained from *C. arboreaa*, rich in phenolic compounds with a good antioxidant properties, shows anticoagulant activity comparable to that of warfarin, an anticoagulant commonly used to treat blood clots such as deep vein thrombosis and pulmonary embolism (66), by increasing APTT, PT and TT (67). This anticoagulant activity is correlated with the high level of gallic acid, 3,4-dihydroxybenzoic acid, quercetin 3-O-glucopyranoside, kaempferol 3-Oglucopyranoside and qurcetin 3-O-(6-O-glucopyranosyl)-gluco pyranoside (68).

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Lines 288-306: 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 (79-81). 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 cAMP generation. These findings suggest that caffeic acid might be an excellent starting point for the development of novel therapeutic agents for thrombotic disorders (82).
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 (83).
The results of *in vitro* and *ex vivo* coagulation studies show that APTT was significantly prolonged and the PT was delayed also by quercetin (84). Moreover, bioinformatic analyses reported by Bijak et al (85) 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 (85).

Lines 323-326: 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 (90).

Lines 331-378: 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 (91). 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 antithrombin III. EuRP-61 may influence all the three pathways of human coagulation cascade, ie 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 (91).
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 (92). Studies regarding the bioactivity of European broomrapes (*O. caryophyllacea*, *P. arenaria*, *P. ramosa*) and single isolated phenylpropanoid glycosides, 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 (92).
Licania rigida Benth crude leaf extract (CELR) and ethyl acetate fraction (AFLR) demonstrated to possess *in vitro* anticoagulant activity (93). In particular, the extracts are able to prolonge 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 (93). 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 (94). This implies that a plant extract may provide a favorable response compared to the use of a single compound (95).

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 (96). 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 (96).
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 prolonge clotting time-APTT and to inhibit by 48% the ADP-induced platelet aggregation (97). 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 (97).
Polyphenolic–polysaccharide (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 (98).

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.

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 (65-68)	gallic acid, 3,4-dihydroxybenzoic acid, quercetin 3-O-glucopyranoside, kaempferol 3-Oglucopyranoside, quercetin 3-O-(6-O-glucopyranosyl)-gluco pyranoside	*in vitro* prolongation of APTT, PT and TT
Rosmarinus officinalis (69-76)	tritepenes, ursolic acid, oleanolic acid, betulinic acid, carnosol, micromeric acid	*in vitro* prolongation of TT
Thymus atlanticus, Thymus zygis (77-85)	caffeic acid, rosmarinic acid, quercetin, rutin, hyperoside, luteolin-7-*O*-glucoside	*in vitro* prolongation of APTT and PT
Viola yedoensis (86,87)	dimeresculetin	*in vitro* prolongation of APTT, PT and TT
Fragaria vesca, Echinacea purpurea, Erigeron canadensis (88-90)	hexuronic acids and phenolic glycoconjugates	*in vitro* prolongation of APTT and PT
Euphorbia resinifera (91)	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 ramosa (92)	phenylpropanoid glycosides: tubuloside A, poliumoside, 3-*O*-methylpoliumoside	*in vitro* prolongation of APTT, PT and TT
Licania rigida (93-95)	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 (96)	phenolics and flavonoids	*in vitro* prolongation of APTT and PT
Genipa americana (97)	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 (98)	olyphenolic–polysaccharide conjugates	*in vitro* prolongation of APTT and PT

Comment 8: Line 264 (now line 263) – I suggest removing or changing this sentence. The "believing" is wrong when there is described assays to proving or suggesting possible mechanisms of action, well described and presented in literature.
Reply 8: the sentence was modified.
Changes in the text: *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.

Comment 9: Please, inform that "Rosemary" is a popular name for *Rosmarinus officinalis*.
Reply 9: the sentence has been modified (line 264).
Changes in the text: the popular name of *R. officinalis*

Comment 10: Line 275 (now line 282) – How many species? Please, inform.
Reply 10: The number of species has been added.
Changes in the text: The family *Thymus* includes about 350 species of aromatic perennial herbaceous plants

Comment 11: Line 306 – "in purified form": There was no purified flavonoid or polyphenol derivatives presents in the text. There is a lack of important information about these compounds including the activity. In this way the comparison of both, extracts and pure compounds, in relation of biological activities can reinforce the arguments for the potential of plants and in the treatment of coagulation disorders in COVID-19 disease. This is an important discussion to perform in your paper. Please, provide more prototypes information as possible.
Reply 11: the sentence, now removed, referred to commercial preparation of food supplements based on flavonoid or polyphenol. In the text the bioactivity of purified compounds involved in the anticoagulant activity of extracts have been added.
Changes in the text: the following sentence has been removed "as well as the polyphenols and flavonoids in purified form". A discussion of bioactivity of isolated anticoagulant compounds has been added as evidenced in Reply 7.

Reviewer B
Comment 1: I suggest including the terms "polyphenols, flavonoids and polyphenols/flavonoids anticoagulants" as keywords for searching in the databases (Research Method). As the author describes that these classes of molecules present anticoagulant properties, including theses terms could increase the number of plant extracts and molecules with this biological activity.
Reply 1: the terms suggested have been included as keywords for searching in the databases.
Changes in the text: lines 80-81 or "polyphenols, flavonoids and polyphenols/flavonoids anticoagulants"

Comment 2: Line nº249 (now line 245): The author cites 2 references regarding to anticoagulant molecules and food anticoagulants. However, these references do not cover up the topics highlighted. I suggest citing some natural products reviews about anticoagulant molecules and food additives that could act as anticoagulants. To sum up, to enrich this discussion.
Reply 2: references covering up the topics have been added.
Changes in the text: added the following references:

62 Keihanian F, Saeidinia A, Bagheri RK, Johnston TP, Sahebkar A. Curcumin, hemostasis, thrombosis, and coagulation. J Cell Physiol. 2018 Jun;233(6):4497-4511. doi: 10.1002/jcp.26249. Epub 2017 Dec 26. PMID: 29052850.

63 Ryu JH, Kang D. Physicochemical Properties, Biological Activity, Health Benefits, and General Limitations of Aged Black Garlic: A Review. Molecules. 2017 Jun 1;22(6):919. doi: 10.3390/molecules22060919. PMID: 28587168; PMCID: PMC6152780.

Comment 3: Line nº 253 (now line 249): A reference about the specie *Careya arborea* as well as its occurrence is missing.
Reply 3: the reference has been added.
Changes in the text: added the following reference:

64. Kumar Satish BN, Swami Vrushabendra BM, Kumar GK, Gobinda B. Review on *Careya arborea* Roxb. *Int J Res In Ayurveda Pharm.* 2010;1(2):306–315.

Comment 4: Line nº 260 (now line 259): The description of Rosmarinus officinalis lacks references.
Reply 4: reference has been added
Changes in the text: the following reference has been added:

69. Borges RS, Ortiz BLS, Pereira ACM, Keita H, Carvalho JCT. Rosmarinus officinalis essential oil: A review of its phytochemistry, anti-inflammatory activity, and mechanisms of action involved. J Ethnopharmacol. 2019 Jan 30;229:29-45. doi: 10.1016/j.jep.2018.09.038. Epub 2018 Oct 2. PMID: 30287195.

Comment 5: Line nº 275 (now line 282): The description of the genus Thymus also lacks references.
Reply 5: reference has been added.
Changes in the text: the following reference has been added:

77. Nabavi SM, Marchese A, Izadi M, Curti V, Daglia M, Nabavi SF. Plants belonging to the genus Thymus as antibacterial agents: from farm to pharmacy. Food Chem. 2015 Apr 15;173:339-47. doi: 10.1016/j.foodchem.2014.10.042. Epub 2014 Oct 25. PMID: 25466031.

Comment 6: Line nº 294 and 295: It would enrich the discussion if the author described the phytochemicals isolated.
Reply 6: The discussion based on phytochemical isolated has been improved.
Changes in the text: Lines 323-326: 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 (90).

Comment 7: In general, I suggest increasing the discussion about extracts and isolated compounds with anticoagulant properties that could be used in Covid-19 treatment. It is clear that the intention of the author is to describe plants and extracts as potential use in anticoagulant treatments. However, including classes of metabolites as well as its isolates, or even the major compounds responsible for the bioactivity, could enrich the discussion of the article. In addition, a wider research about anticoagulant extracts could increase the number of species listed. In my perspective, the number of species cited is insufficient. To achieve this, the authors should take into consideration articles published before 2020 as well. Finally, I suggest the creation of a table to gather all the species cited, class of metabolites, isolated metabolites (if possible) and bioactivity.
Reply 7: discussion has been improved as suggested. Class of metabolites with anticoagulant activity have been added. The number of species cited has been improved. Publication up to 2021 have been considered. The table (Table 1) has been added as well as references suggested by the Referee.
Changes in the text: the following sentences have been added in order to improve the manuscript, as suggested by the Referee.

> Lines 253-258: The methanolic extract obtained from *C. arboreaa*, rich in phenolic compounds with a good antioxidant properties, shows anticoagulant activity comparable to that of warfarin, an anticoagulant commonly used to treat blood clots such as deep vein

thrombosis and pulmonary embolism (66), by increasing APTT, PT and TT (67). This anticoagulant activity is correlated with the high level of gallic acid, 3,4-dihydroxybenzoic acid, quercetin 3-O-glucopyranoside, kaempferol 3-Oglucopyranoside and qurcetin 3-O-(6-O-glucopyranosyl)-gluco pyranoside (68).

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(77-85)	7-*O*-glucoside	and PT
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Pseuderanthemum palatiferum (98)	olyphenolic–polysaccharide conjugates	*in vitro* prolongation of APTT and PT

The following references have been added as suggested by Referee:

- https://doi.org/10.1016/j.cbi.2016.07.022: reference n. 60
- https://doi.org/10.1016/j.cbi.2020.109223: reference n. 91
- https://doi.org/10.1016/j.ijbiomac.2014.01.023: reference n. 85
- https://doi.org/10.1016/j.ijbiomac.2020.04.113: reference n. 98
- https://doi.org/10.1016/j.carbpol.2018.09.003: reference n. 97
- https://doi.org/10.1016/j.sajb.2020.01.014: reference n. 96
- https://doi.org/10.1016/j.sajb.2021.02.016: reference n. 93
- https://doi.org/10.1016/j.biopha.2021.111618: reference n. 92