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Mechanisms and interactions in concomitant use of herbs and warfarin therapy: An updated review

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ABSTRACT

This review is an updated and expanded version published in this journal in 2016. Warfarin pharmacotherapy is extremely complex, since in addition to being a low therapeutic index drug, it does not follow the dose-response pattern and has characteristics that predispose the occurrence of interactions, such as high binding rate to plasma proteins, metabolization by cytochrome P450 enzymes, further to acting in the complex process of blood coagulation, platelet activation, and inflammation. For these reasons, warfarin has great potential for interaction with drugs, foods, and herbal medicines. Herb-warfarin interactions, however, are still not very well studied; thus, the objective of this update is to present new information on the subject aiming to provide a scientific basis to help health professionals in the clinical management of these interactions. A literature review was performed from May to June 2021 in multiple databases and articles published in 2016 to 2021 were included. A total of 59 articles describing 114 herbal medicines were reported to interact with warfarin. Of the plants mentioned, 84% had the potential to increase warfarin effect and the risk of bleeding. Targets possibly involved in these interactions include the processes of blood coagulation, platelet activation, and inflammation, in addition to the pharmacokinetics and pharmacodynamics of warfarin. Despite these alarming numbers, however, the clinical management of interactions is known to be effective. Thus, it is important that the use of these herbal medicines be done with caution in anticoagulated patients and that studies of herb-drug interactions be encouraged in order to generate information to support the clinical management of patients.

1. Introduction

It has been about 5 years since the publication of our first review on the mechanisms and interactions in the concomitant use of herbs and warfarin [1] and, during these years, much has evolved in this area of knowledge, with new applications for plants that act on hemostasis. Some observational studies have been published demonstrating the high prevalence of unsupervised use of herbal medicines, a situation that facilitates the occurrence of adverse reactions [2]. One of these studies, in which the use of herbal medicines was observed by almost 70% of the participants, was carried out with patients undergoing anticoagulation with warfarin [3]. Another study was carried out with patients with kidney disease, a condition that enhances the severity of interactions. Detected in this study was a prevalence of 18.6% of concomitant use of herbal medicines and drugs, and ginseng was the plant most implicated in these interactions, being involved in 6 cases of severe interaction with antithrombotics. [4]. Other studies have also shown that herb-drug interactions are a major clinical concern, constituting a public health problem, as they can lead to serious adverse events such as intense bleeding, prolonged hospitalization, and even death [5,6].

In addition to the appreciation of this theme since the 1980 s, when the term herb-drug interaction started to appear in literature [7], it is also noted that other targets of interaction have been elucidated. Until 2016, most interaction studies involved cytochrome P450 [1].

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Currently, other targets have been widely studied, such as renal, intestinal, and hepatocellular transporters, in addition to albumin receptors, involved in the distribution of drugs such as warfarin [8–10]. The techniques used to study potential interactions have also evolved in recent years. Several types of computational studies, such as molecular docking, have been used for this purpose. These studies make it possible to study the interaction of substances from herbal medicines with molecular targets, present in inflammation, platelet aggregation, and coagulation cascade pathways [9,11]. Another innovation is the use of the thrombin generation assay (TGA) to study blood coagulation to replace prothrombin (PT) and activated partial thromboplastin (aPPT) tests. In addition to being more robust, the TGA allows a more complete assessment of blood clotting [12,13].

Even with so many advances, the most reported interaction in adults is still the risk of bleeding due to the use of antithrombotics in conjunction with garlic, ginkgo, ginger, and ginseng. And among the antithrombotic drugs, the highlight still is warfarin [1,5,6]. However, interactions involving direct oral anticoagulants, rivaroxaban, are already being elucidated [14–16]. Furthermore, warfarin interactions with other plant species have been elucidated in recent years, such as *Cannabis sativa* [17], some herbal preparations from Traditional Chinese Medicine (TCM) [18], and others. Along with the development of these interaction studies, there was also an evolution of studies on the potential of these plants for the development of antithrombotics [19–22]. These two themes are sides of the same coin; that is, a plant that has the potential to interact with warfarin, increasing its effect, can per se be a candidate for an anticoagulant [12,13]. In this sense, plants in this context were studied, aiming, for example, for their use in the prevention of atherosclerosis [23] and in the creation of materials for implants that come into contact with blood, such as cardiac patches and grafts [24,25], since anticoagulant activity is desirable in both cases.

Meanwhile, although more plants have been studied for their potential to interact with drugs and the evolution of techniques for that study, information on herb-drug interaction remains based mainly on in vitro and in vivo animal and case reports [26]. Considering the multifactorial nature involved in the occurrence of these interactions, it is still a challenge to predict the clinical outcome in this situation. Furthermore, the study of the effect of herbal medicines on patients is complex due to ethical issues. Therefore, efforts have been made to create models that help to extrapolate the results of these studies to clinical practice, aiming to assist in the clinical management of herb-drug interactions [27]. In addition, the pharmacovigilance in concomitant use of anticoagulants and herbal medicines, although very important, still needs to be greatly expanded to generate data on the subject [28]. Thus, considering the safety limitations associated with the use of warfarin, the purpose of this update is to gather new information about potential interactions between warfarin and herbal medicines, aiming to provide a scientific basis to assist health professionals in the clinical management of these interactions and contribute to the improvement in patient care (Supplementary material).

2. Methods

This literature review is an updated version of a paper that was published in this journal in 2016. The data were collected in the period from May to July 2021 using various online databases, including PUBMED, LILACS, Onefile, Scopus, SciVerse, Science Direct, Web of Science, Sci-finder, MEDLINE, Springerlink, Directory of Open Acess Journals, Biomed Central, SciELO, American Chemical Society, Sage Publications, and Wiley Online Library. The keywords used were 'warfarin' or 'anticoagulants' combined with 'herbs' or 'plants', and 'interaction'. Articles published from 2016–2021 were selected, since the previous review covered publications until 2015. About 1700 articles were found and these were pre-selected according to title and abstract. All articles that contained some information regarding the possibility of warfarin interacting with herbal medicines were included and studies evaluating the effect of isolated substances or substances from marine organisms were excluded, resulting in 171 articles. After reading their full text, 59 articles met the selection criteria and were included in this review. The following data were extracted from the included studies: the scientific and common name, type of plant derivative studied and family of the medicinal plant, information on interaction with warfarin, associated consequences, and source of evidence. The scientific name was used according to the Missouri Botanical Garden classification through the website worldfloraonline.org. Due to the scarcity of clinical studies evaluating herbs-warfarin interaction, as in the previous review, secondary data sources were included in order to cover a greater amount of information on the topic. After the compilation of the literature data, we critically reviewed the data and analyzed the information, aiming to identify the chemical substances and targets of interaction involved in warfarin interaction.

3. Results

In the update period (2016–2021), the search identified a total of 1794 articles, and 171 articles were identified from screening of title and abstract. Of these, 104 articles were excluded as they did not meet the selection criteria and 59 articles were included in this update. These studies covered possible interactions of 114 plant species with warfarin (Table 1). Most of these herbal medicines (84%) have the potential to increase warfarin effect, then the risk of bleeding. Another 10 plants have the potential to reduce warfarin effect; 6 plants can act, by different mechanisms, in both directions; and 2 plants increase and decrease the effect of these drugs according to the dose or exposure time (Table 1).

Among the possible targets of bioactive substances that enable the interaction with warfarin, platelet activation (35% of the listed herbs), blood coagulation (27%), and pharmacokinetics (21%) stand out, mainly in the metabolism phase. Other known targets are the inflammation pathway and the warfarin target, the enzyme vitamin K-oxide reductase (VKOR) (Table 1). The mechanisms involved in platelet activation mainly include inhibition of platelet aggregation, but also inhibition of platelet adhesion and secretion. In coagulation, most plants act in an unspecific way in the intrinsic and extrinsic pathways, and the coagulation factors involved have not been determined. In the inflammation pathway, the described mechanisms involve inhibition of the arachidonic acid pathway, reducing thromboxane A2 (TXA2) and cyclooxygenase (COX), for example. Finally, in relation to warfarin pharmacokinetics, most of the evidence refers to the inhibition or induction of cytochrome P450 enzymes, but there is also evidence of alteration in the processes of absorption (intestinal transporters), distribution (binding to albumin), and secretion (renal transporters) (Table 1).

With regard to scientific evidence, most were reviews (secondary sources). However, there was a significant presence of in vitro studies in humans (16%) and in vivo studies in animals (17%), including rats and mice. We also found 4 case reports and 3 molecular docking studies (Table 1).

4. Discussion

Warfarin is an oral anticoagulant widely used to prevent thromboembolic disorders. This anticoagulant acts on blood coagulation, which itself is a complex pathway, and its activity occurs in the extrinsic and intrinsic pathways through effects on vitamin K-dependent clotting factors (II, VII, IX, and X) and the anticoagulant proteins C and S [1,3,80]. In addition, warfarin is a drug with complex pharmacotherapy, especially with regard to safety parameters, one of which is the potential for interaction. For these reasons, patients using warfarin require constant monitoring by health professionals, and anticoagulation clinics are excellent options to improve the outcome of this pharmacotherapy [3,12,81]. In the clinical management of these patients, however, the evaluation of herb-warfarin interaction does not happen very often, and

Table 1
Potential herbal interaction with warfarin and the involved targets.

Scientific name	Common name	Family	Evaluated plant derivative	Pathway target	Mechanism	Possible outcome in concomitant use with warfarin	Source of evidence	Reference
Acacia senegal (L.) Willd.	Gum arabic	Fabaceae	Resin	Coagulation cascade	Prolonged PT	Increase the risk of bleeding	Animais (mice)	[29]
				Platelet activation	Increased platelet aggregation			[29]
Aesculus hippocastanum L.	Horse chestnut	Sapindaceae	NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[14]
Ajuga bracteosa Wall. ex Benth.	Bugle	Lamiaceae	Chloroform extract of aerial part and root	Coagulation cascade	Prolonged clotting time (capillary tube method)	Increase the risk of bleeding	Animais (rats)	[30]
Allium cepa L.	Onion	Amaryllidaceae	Various	Platelet activation	Decreased platelet adhesion and aggregation; Decreased TXA2 synthesis	Increase the risk of bleeding	Review	[1,31]
Allium sativum L.	Garlic	Amaryllidaceae	NA	Platelet activation	Decreased platelet aggregation by inhibiting PAF and fibrinogen receptors; decreased TXA2 synthesis	Increase the risk of bleeding	Review	[1,32,33]
			CAM Product					[34]
			Various					[31]
			NA					[14]
			NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[1]
Aloe vera (L.) Burm.f.	Aloe	Xanthorrhoeaceae	NA	Pharmacokinetics	Decreased warfarin intestinal absorption and/or increased warfarin renal clearance	Decrease warfarin effect	Review	[1,14]
			NA	–	Non-described mechanism based on a case report	Increase the risk of bleeding	Review	[32]
Alpinia galanga (L.) Willd.	Galanga	Zingiberaceae	NA	Platelet activation	PAF inhibition	Increase the risk of bleeding	Review	[1]
Andrographis paniculata (Burm.f.) Nees	Kariyat	Acanthaceae	NA	Platelet activation	Decreased platelet aggregation (andrographolide)	Increase the risk of bleeding	Review	[33]
Angelica sinensis (Oliv.) Diels	Dong quai	Apiaceae	NA	Coagulation cascade	Prolonged PT	Increase the risk of bleeding	Review	[32]
			NA	Platelet activation	Decreased serotonin and ADP release from platelets			[14]
			NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[1,33]
Arctium lappa L.	Burdock	Compositae	NA	Platelet activation	PAF inhibition (lignans and sesquiterpenes)	Increase the risk of bleeding	Review	[1]
Arnica montana L.	Mountain arnica	Compositae	NA	Platelet activation	Decreased platelet aggregation via ADP	Increase the risk of bleeding	Review	[1]
Aronia melanocarpa (Michx.) Britton	Chokeberry	Rosaceae	NA	Coagulation cascade	Prolonged TT, PT and aPTT	Increase the risk of bleeding	Review	[21]
			NA	Platelet activation	Decreased platelet aggregation; decreased TXA2 synthesis			[35]
Artemisia absinthium L.	Absinth wormwood	Compositae	NA	–	Non-described mechanism based on a case report	Increase the risk of bleeding	Review	[33,34]
Astilbe chinensis (Maxim.) Franch. & Sav.	False goat's beard	Saxifragaceae	Aerial part methanolic extract	Platelet activation	Decreased platelet aggregation, calcium mobilization, granule secretion, and fibrinogen binding to integrin αIIb/β3	Increase the risk of bleeding	Animais (rats)	[36]
Boesenbergia pandurata (Roxb.) Schltr.	Chinese ginger	Zingiberaceae	NA	Platelet activation	PAF inhibition	Increase the risk of bleeding	Review	[1]
Calophyllum L.	True kamani	Calophyllaceae	NA	Platelet activation	PAF inhibition (xanthones)	Increase the risk of bleeding	Review	[1]
Camellia sinensis (L.) Kuntze	Green tea	Theaceae	NA	Inflamation	Decreased arachidonic acid pathway and TXA2 synthesis	Increase the risk of bleeding	Review	[32]
			NA	Warfarin receptor	High vitamin K content		Review	[32,33]

(*continued on next page*)

Table 1 (*continued*)

Scientific name	Common name	Family	Evaluated plant derivative	Pathway target	Mechanism	Possible outcome in concomitant use with warfarin	Source of evidence	Reference
						Decrease warfarin effect		
			NA					[37]
			NA					[38]
			NA					[39]
			NA					[14]
Cannabis sativa L.	Marijuana	Cannabaceae	ND	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Case report	[33,40]
			ND	–	Non-described mechanism	Increase the risk of bleeding	Case report	[17]
Carica papaya L.	Papaya	Caricaceae	NA	–	Non-described mechanism based on a case report	Increase the risk of bleeding	Review	[33]
Carthamus tinctorius L.	Safflower	Compositae	Commercially obtained injection	Coagulation cascade	Prolonged PT and aPTT	Increase the risk of bleeding	Animais (rats)	[41]
				Pharmacokinetics	CYP inhibition			
			NA	–	Non-described mechanism based on a case report	Increase the risk of bleeding	Review	[33]
Cassia abbreviata Oliv.	Sjambok pod	Fabaceae	Aqueous extract	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	In vitro	[42]
Centipeda minima (L.) A.Braun & Asch.	Spreading sneeze	Compositae	NA	Platelet activation	PAF inhibition (lignans and sesquiterpenes)	Increase the risk of bleeding	Review	[1]
Cinnamomum sp	–	Lauraceae	NA	Platelet activation	PAF inhibition	Increase the risk of bleeding	Review	[1]
Centella asiatica	Kotu kola		NA		CYP inhibition	Increase the risk of bleeding	Review	[33]
Citrus paradisi Macfad.	Grapefruit	Rutaceae	NA	Platelet activation	Decreased platelet adhesion, aggregation and secretion; decreased TXA2 synthesis	Increase the risk of bleeding	Review	[35]
			NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[32,33]
			NA					[37]
			NA					[38]
			NA					[14]
Clerodendrum colebrookianum Walp.	East Indian glory bower	Lamiaceae	Leave extracts with different solvents	Coagulation cascade	Prolonged PT and aPTT; reduced fibrinogen formation	Increase the risk of bleeding	In vitro	[43]
				Platelet activation	Decreased collagen/ADP-induced platelet aggregation			
				–	Antithrombotic effect in thrombosis model	Increase the risk of bleeding	Animais (mice)	[43]
Colubrina arborescens (Mill.) Sarg.	Mauby	Rhamnaceae	Drink made from the bark	–	Non-described mechanism	Increase the risk of bleeding	Case report	[44]
Commiphora molmol (Engl.) Engl. ex Tschirch	Myrrh	Burseraceae	NA	–	Non-described mechanism based on a case report	Decrease warfarin effect	Review	[33,34]
			NA					[6]
Corydalis decumbens (Thunb.) Pers.	Jirobo-engosaku	Papaveraceae	Commercially obtained injection	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Animais (rats)	[45]
Crassocephalum crepidioides (Benth.) S. Moore	Redflower ragleaf	Compositae	Leaf methanol extract	Coagulation cascade	Prolonged CT, BT, PT and aPTT	Increase the risk of bleeding	Animais (rats)	[46]
				Coagulation cascade	Prolonged CT, PT and aPTT	Increase the risk of bleeding	In vitro	[47]
Crataegus monogyna Jacq.	Hawthorn	Rosaceae	NA	Platelet activation	Decreased TXA2 synthesis	Increase the risk of bleeding	Review	[1]
Crocus sativus L.	Saffron	Iridaceae	Ethanol/water (80%, v/v) extract	Coagulation cascade	Prolonged clotting time (capillary tube method)	Increase the risk of bleeding	Animais (mice)	[48]
			NA	Inflamation	Downregulated several pro-inflammatory mediators	Increase the risk of bleeding	Review	[49]
Curcuma longa L	Turmeric	Zingiberaceae	NA	Platelet activation	PAF inhibition	Increase the risk of bleeding	Review	[1,33]

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Table 1 (*continued*)

Scientific name	Common name	Family	Evaluated plant derivative	Pathway target	Mechanism	Possible outcome in concomitant use with warfarin	Source of evidence	Reference
			NA	Inflamation	Decreased arachidonic acid pathway and TXA2 synthesis	Increase the risk of bleeding	Review	[32]
Cymbopogon citratus (DC.) Stapf	Lemon grass	Poaceae	NA	–	Non-described mechanism based on a case report	Decrease warfarin effect	Review	[33]
Echinacea purpurea (L.) Moench	Echinaceae	Compositae	NA	Coagulation cascade	Prolonged PT and aPTT	Increase the risk of bleeding	Review	[21,33]
Erigeron breviscapus (Vaniot) Hand.-Mazz.	Lifeflower	Compositae	Whole plant aqueous extract	Coagulation cascade	Prolonged PT.	Increase the risk of bleeding	Animais (rats)	[50]
				Pharmacokinetics	Cmax, AUC and t1/2 prolonged significantly			
Eucalyptus globulus Labill.	Eucalyptus	Mytaceae	NA	–	Non-described mechanism	Increase the risk of bleeding	Review	[14]
Fagonia cretica L.	Virgin's mantle	Zygophyllaceae	Methanol/ chloroform (1:1) extract	Coagulation cascade	Prolonged clotting time (capillary tube method)	Increase the risk of bleeding	Animais (rats)	[51]
Filipendula ulmaria (L.) Maxim.	Meadowsweet	Rosaceae	NA	Platelet activation	Antiplatelet effects due to the presence of salicylates	Increase the risk of bleeding	Review	[32]
Foeniculum vulgare Mill.	Fennel	Apiaceae	NA	–	Non-described mechanism	Increase the risk of bleeding	Review	[14]
Forsythia suspensa (Thunb.) Vahl	Golden bells	Oleaceae	NA	Platelet activation	PAF inhibition (lignans and sesquiterpenes)	Increase the risk of bleeding	Review	[1]
Fragaria × *ananassa* Duchesne	Strawberry	Rosaceae	NA	Platelet activation	Decreased platelet aggregation	Increase the risk of bleeding	Review	[35]
Fragaria vesca Benth.	Wild strawberry	Rosaceae	NA	Coagulation cascade	Prolonged PT and aPTT	Increase the risk of bleeding	Review	[21]
Galium verum L.	Lady's bedstraw	Rubiaceae	Ethanol extract	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Animais (rats)	[52]
Garcinia cambogia (Gaertn.) Desr.	Garcinia	Clusiaceae	NA	Platelet activation	Decreased platelet adhesion, aggregation and secretion (flavonoids)	Increase the risk of bleeding	Review	[1]
Ginkgo biloba L.	Ginkgo	Ginkgoaceae	NA	Platelet activation	PAF inhibition (Ginkgolide B)	Increase the risk of bleeding	Review	[1,32]
			NA					[33,38]
			NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[14]
			NA					[37]
			NA					[38]
			CAM product					[34]
Glycine max (L.) Merr.	Soybean	Fabaceae	NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[38]
			NA					[33,37]
			NA	Pharmacokinetics	Alterations of P-gp/OATP transporters	Decrease warfarin effect	Review	[10]
			NA	Warfarin receptor	High vitamin K content	Decrease warfarin effect	Review	[14]
			NA					[38]
Glycyrrhiza glabra L.	Liquorice	Fabaceae	NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[1,33]
Goniothalamus malayanus Hook. f. & Thomson	–	Annonaceae	NA	Platelet activation	PAF inhibition	Increase the risk of bleeding	Review	[1]
Harpagophytum procumbens (Burch.) DC. ex Meisn.	Devil's claw	Pedaliaceae	NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[1,33]
Hedera nepalensis K.Koch	Himalayan ivy	Araliaceae	Methanol/ chloroform (1:1) extract	Coagulation cascade	Prolonged clotting time (capillary tube method)	Increase the risk of bleeding	Animais (rats)	[51]
Hippophae rhamnoides L.	Bea buckthorn berries	Elaeagnaceae	NA	Platelet activation	Decreased platelet adhesion and aggregation; decreased TXA2 synthesis	Increase the risk of bleeding	Review	[35]
Hypericum patulum Thunb.	Hidcote	Hypericaceae	NA	Platelet activation	PAF inhibition (xanthones)	Increase the risk of bleeding	Review	[1]
Hypericum perforatum L.	St John's wort	Hypericaceae	NA	Pharmacokinetics	CYP induction	Decrease warfarin effect	Review	[33,37]

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Table 1 (*continued*)

Scientific name	Common name	Family	Evaluated plant derivative	Pathway target	Mechanism	Possible outcome in concomitant use with warfarin	Source of evidence	Reference
			NA					[38]
			Tablet					[34,53]
			NA					[14]
			NA	–	Non-described mechanism based on a case report	Increase the risk of bleeding	Review	[6]
Juniperus sargentii (A.Henry) Takeda ex Nakai	Juniper	Cupressaceae	NA	Warfarin receptor	High vitamin K content	Decrease warfarin effect	Review	[14]
Leonurus cardiaca L.	Motherwort	Lamiaceae	Acetone-water extract	Platelet activation	Decreased platelet aggregation	Increase the risk of bleeding	In vitro	[1,54]
Linum usitatissimum L.	Flaxseed	Linaceae	Buffer extract	Coagulation cascade	Prolonged PT and aPTT	Increase the risk of bleeding	In vitro	[55]
				Platelet activation	Decreased platelet aggregation via ADP and adrenaline			
			NA	Platelet activation	Linolenic acid is believed to cause changes in the composition of the platelet membrane	Increase the risk of bleeding	Review	[32]
Liquidambar orientalis Mill.	Styrax liquidus	Altingiaceae	Standard extract	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	In vitro	[56]
Lycium barbarum Mill.	Gogi berry	Solanaceae	NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[1,6,33]
			NA					[14]
			Juice, water, and ethanol extracts				In vitro	[57]
Mangifera indica L.	Mango	Anacardiaceae	NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[1,33,38]
			NA					[14]
Matricaria chamomilla L.	Chamomile	Compositae	Essential oil	Coagulation cascade	Prolonged aPTT	Increase the risk of bleeding	In vitro	[25]
			NA	Coagulation cascade	Anticoagulant effect due to the presence of coumarins (speculation)	Increase the risk of bleeding	Review	[32]
			NA	Coagulation cascade	Non-described mechanism based on a case report	Increase the risk of bleeding	Review	[6]
			Essential oil	Platelet activation	Decreased platelet adhesion	Increase the risk of bleeding	In vitro	[25]
			NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[1,33,38]
Medicago sativa L.	Lucerne	Fabaceae	NA	Pharmacokinetics	Decreased warfarin intestinal absorption and/or increased warfarin renal clearance	Decrease warfarin effect	Review	[14]
Melilotus officinalis (L.) Pall.	Sweet clover	Fabaceae	NA	Coagulation cascade	Contains coumarin, which is converted to dicoumarol (2 case reports)	Increase the risk of bleeding	Review	[33]
Mentha crispa L.; *Menhta spicata* L.; *Mentha viridis* (L.) L.	Spearmint	Lamiaceae	Ethanol extract	Coagulation cascade	Prolonged PT and aPTT; decreased thrombin generation	Increase the risk of bleeding	In vitro	[58]
			Essential oil	Coagulation cascade	Prolonged PT	Increase the risk of bleeding	In vitro	[59]
Mentha pulegium L.	Pennyroyal	Lamiaceae	Essential oil	Coagulation cascade	Alteration in PT	Variable by dose	In vitro	[59]
Mentha x piperita L.	Peppermint	Lamiaceae	NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[33]
Mikania laevigata Sch.Bip. ex Baker	Guaco	Compositae	Ethanol extract	Coagulation cascade	Prolonged PT and aPTT; decreased thrombin generation	Increase the risk of bleeding	In vitro	[12]
Momordica charantia L.	Bitter melon	Cucurbitaceae	NA	Coagulation cascade	Decreased activation of factor X	Increase the risk of bleeding	Review	[1]
				Platelet activation	PAF inhibition			
Moringa oleifera Lam.	Moringa	Moringaceae	NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[33]
Morus alba L.	Mulberry	Moraceae	Ethanol extract	Platelet activation	Decreased platelet aggregation, granule	Increase the risk of bleeding	Animais (rats)	[60]

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Table 1 (*continued*)

Scientific name	Common name	Family	Evaluated plant derivative	Pathway target	Mechanism	Possible outcome in concomitant use with warfarin	Source of evidence	Reference
					secretion, [Ca2 +] release, and integrin α/β activation			
Newbouldia laevis (P.Beauv.) Seem.	Boundary tree	Bignoniaceae	Aqueous extract	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	In vitro	[42]
Ocimum basilicum L.	Basil	Lamiaceae	NA	Platelet activation	Decreased platelet aggregation ADP-induced and platelet actvation by thrombin	Increase the risk of bleeding	Review	[1]
Oenothera biennis L.	Evening primrose	Onagraceae	NA	Coagulation cascade	Prolonged BT	Increase the risk of bleeding	Review	[42]
			NA	Platelet activation	Decreased platelet aggregation; decreased TXA2 synthesis	Increase the risk of bleeding	Review	[42]
Origanum vulgare L.	Oregano	Lamiaceae	NA	–	Non-described mechanism	Increase the risk of bleeding	Review	[42]
Paeonia L.	Peony	Paeoniaceae	NA	Platelet activation	Antiplatelet effect	Increase the risk of bleeding	Review	[1]
Panax ginseng C.A. Mey.	Ginseng	Araliaceae	Methanol extract	Coagulation cascade	Activated blood coagulation factors II, VII and protein Z	Decrease warfarin effect	Animais (rats)	[61]
			NA	Coagulation cascade	Factor Xa inhibition	Increase the risk of bleeding	Docking	[62]
			Ethanol extract				In vitro	[62]
			NA	Platelet activation	Decreased platelet aggregation via PAF; decreased TXA2 synthesis	Increase the risk of bleeding	Review	[32]
			CAM product					[34]
			NA					[38]
			NA					[63]
			NA					[64]
			Supplement	Pharmacokinetics	CYP induction	Decrease warfarin effect	Review	[34]
			Methanol extract					[61]
			NA					[65]
			NA					[37]
			NA					[38]
			NA					[14]
Passiflora edulis Sims	Passionfruit	Passifloraceae	NA	Warfarin receptor	High vitamin K content	Decrease warfarin effect	Review	[14]
Persea americana Mill.	Avocado	Lauraceae	NA	Warfarin receptor	High vitamin K content	Decrease warfarin effect	Review	[33]
Petiveria alliacea L.	Guinea Hen Weed	Phytolaccaceae	Leave aqueous extract	Coagulation cascade	Prolonged TT	Increase the risk of bleeding	In vitro	[66]
Peumus boldus Molina	Boldo	Monimiaceae	NA	–	Non-described mechanism based on a case report	Increase the risk of bleeding	Review	[33]
Phoenix dactylifera L.	Date palm	Arecaceae	Ethanol extract	Coagulation cascade	Prolonged BT and PT	Increase the risk of bleeding	Animais (mice)	[67]
Phytolacca latbenia (Moq.) H. Walter	–	Phytolaccaceae	Methanol/ chloroform (1:1) extract	Coagulation cascade	Prolonged clotting time (capillary tube method)	Increase the risk of bleeding	Animais (rats)	[51]
Piper aduncum L.	Spiked pepper	Piperaceae	NA	Platelet activation	PAF inhibition	Increase the risk of bleeding	Review	[1]
Piper kadsura (Choisy) Ohwi	Haifenteng	Piperaceae	NA	Platelet activation	PAF inhibition (furano lignans and kadsurenone)	Increase the risk of bleeding	Review	[1]
Piper methysticum G.Forst.	Kava	Piperaceae	NA	Platelet activation	Decreased platelet aggregation, endogenous ATP release, formation of TXA2, PGE2 and COX-2	Increase the risk of bleeding	Review	[1]
Plantago ovata Forssk.	Psillium	Plantaginaceae	NA	Pharmacokinetics	Decreased warfarin intestinal absorption and/or increased warfarin renal clearance	Decrease warfarin effect	Review	[1,14]
Plumbago indica L.	Indian leadwort	Plumbaginaceae	Methanol extract of the root	Pharmacokinetics	CYP induction	Decrease warfarin effect	Animais (mice)	[68]
Pogostemon cablin (Blanco) Benth.	Patchouli	Lamiaceae	Leaves essential oil	Platelet activation	Altered platelet activity differently according to exposure time	Variable by dose	Animais (rats)	[69]
Psidium guajava L.	Guava	Myrtaceae	Leaves extract		Prolonged PT			[70]

(*continued on next page*)

Table 1 (*continued*)

Scientific name	Common name	Family	Evaluated plant derivative	Pathway target	Mechanism	Possible outcome in concomitant use with warfarin	Source of evidence	Reference
				Coagulation cascade		Increase the risk of bleeding	Animais (rats)	
				Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Animais (rats)	[70]
Pueraria lobata (Willd.) Ohwi	Kudzu	Fabaceae	Commercially obtained granules	Pharmacokinetics	CYP induction	Decrease warfarin effect	Animais (rats)	[71]
				Warfarin receptor	Increased the activity, mRNA and protein expression of VKOR			[71]
Punica granatum L.	Pomegranate	Lythraceae	Peel extract	Coagulation cascade	Prolonged PT	Increase the risk of bleeding	Animais (rats)	[70]
			NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[1,14,33]
Salix alba L.	White willow	Salicaceae	NA	Platelet activation	Antiplatelet effects due to the presence of salicylates	Increase the risk of bleeding	Review	[32]
Salvia miltiorrhiza Bunge	Danshen	Lamiaceae	NA	Platelet activation	Antiplatelet effect	Increase the risk of bleeding	Review	[37]
			NA	Pharmacokinetics	Decreased warfarin binding rate to albumin (distribution)	Increase the risk of bleeding	Review	[72]
			NA					[37]
			NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[14]
			NA					[72]
			NA	Pharmacokinetics	CYP induction	Decrease warfarin effect	Review	[37]
Satureja thymbra L.	Savory of Crete	Lamiaceae	Aqueous, methanol and ethanol extracts	Coagulation cascade	Prolonged PT and aPTT	Increase the risk of bleeding	In vitro	[73]
Schisandra chinensis (Turcz.) Baill.	Magnolia-vine	Schisandraceae	Ethanol extract	Platelet activation	Decreased platelet aggregation, granule secretion, [Ca2 +] release, and integrin α/β activation	Increase the risk of bleeding	Animais (rats)	[60]
Serenoa repens (W. Bartram) Small	Saw palmetto	Arecaceae	NA	Inflamation	Decreased COX and arachidonic acid pathway products	Increase the risk of bleeding	Review	[1,32]
			NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[1]
Silybum marianum (L.) Gaertn.	Milk thistle	Compositae	Supplement	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Case report	[33,74]
Solanum xanthocarpum Schrad. & J.C. Wendl.	Yellow-berried Nightshade	Solanaceae	Methanolic leave extract	Coagulation cascade	Decreased thrombin generation	Increase the risk of bleeding	Animais (rats)	[75]
				Platelet activation	Decreased thrombin-induced platelet activation	Increase the risk of bleeding	Animais (rats)	[75]
Spatholobus suberectus Dunn	Ji Xue Tem	Fabaceae	Stem decoction	Platelet activation	Decreased platelet aggregation	Increase the risk of bleeding	In vitro	[76]
Tanacetum parthenium (L.) Sch.Bip.	Feverfew	Compositae	NA	Platelet activation	Decreased platelet aggregation by parthenolide;decreased arachidonic acid pathway activation	Increase the risk of bleeding	Review	[1,32]
Thuja orientalis L.	Thuja	Cupressaceae	NA	Platelet activation	PAF inhibition	Increase the risk of bleeding	Review	[1]
Thymbra spicata L.	Spiked thyme	Lamiaceae	Aqueous, methanol and ethanol extracts	Coagulation cascade	Prolonged PT and aPTT	Increase the risk of bleeding	In vitro	[73]
Tinospora cordifolia (Willd.) Miers	Gurjo	Menispermaceae	Methanolic leave extract	Coagulation cascade	Decreased thrombin generation	Increase the risk of bleeding	Animais (rats)	[75]
				Platelet activation	Decreased platelet adhesion and thrombin-induced platelet activation	Increase the risk of bleeding	Animais (rats)	[75]
Tinospora crispa (L.) Hook. f. & Thomson	Andawali	Menispermaceae	NA	–	Non-described mechanism based on a case report	Increase the risk of bleeding	Review	[33]
Trifolium pratense L.	Red clover	Fabaceae	NA	Coagulation cascade		Increase the risk of bleeding	Review	[32,33]

(*continued on next page*)

Table 1 (*continued*)

Scientific name	Common name	Family	Evaluated plant derivative	Pathway target	Mechanism	Possible outcome in concomitant use with warfarin	Source of evidence	Reference
					Anticoagulant effect due to the presence of coumarins (speculation)			
			NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[1]
Trigonella foenum-graecum L.	Fenugreek	Fabaceae	NA	Coagulation cascade	Anticoagulant effect due to the presence of coumarins (speculation)	Increase the risk of bleeding	Review	[32]
			NA	Platelet activation	Decreased platelet aggregation; decreased TXA2	Increase the risk of bleeding	Review of case reports	[1,6,33]
Uncaria tomentosa (Willd. ex Schult.) DC.	Cat́s claw	Rubiaceae	NA	Coagulation cascade	Decreased thrombin	Increase the risk of bleeding	Docking	[77]
			Ethanolic extract of bark and leaves	Coagulation cascade	Prolonged TT, PT and aPTT	Increase the risk of bleeding	In vitro	[77]
				Platelet activation	Decreased platelet aggregation	Increase the risk of bleeding	In vitro	[77]
Vaccinium macrocarpon Aiton	Cranberry	Ericaceae	NA	Platelet activation	Decreased platelet aggregation	Increase the risk of bleeding	Review	[35]
			NA	Pharmacokinetics	CYP inhibition	Increase the risk of bleeding	Review	[10]
			NA	–	Non-described mechanism	Increase the risk of bleeding	Review	[32,33]
			Fruit juice					[34]
			NA					[38]
			NA					[14]
			Fruit juice					[6]
Vaccinium myrtillus L.	Bilberry	Ericaceae	NA	–	Non-described mechanism based on a case report	Increase the risk of bleeding	Review	[33]
Vaccinium uliginosum L.	Bog blueberry	Ericaceae	NA	Platelet activation	Decreased platelet aggregation	Increase the risk of bleeding	Review	[1]
Verbascum fruticulosum Post	–	Scrophulariaceae	Aqueous, methanol and ethanol extracts	Coagulation cascade	Prolonged PT and aPTT	Increase the risk of bleeding	In vitro	[73]
Verbena officinalis L.	Vervain	Verbenaceae	NA	Warfarin receptor	High vitamin K content	Decrease warfarin effect	Review	[14]
Vitis vinifera L.	Grape	Vitaceae	OMNIVIR®	Coagulation cascade	Prolonged TT, PT and aPTT	Increase the risk of bleeding	In vitro	[78]
			NA				Review	[21]
			OMNIVIR®	Platelet activation	Decreased platelet aggregation	Increase the risk of bleeding	In vitro	[78]
Withania somnifera (L.) Dunal	Indian ginseng	Solanaceae	Aqueous and ethanolic leaf extracts	Platelet activation	Decreased platelet aggregation	Increase the risk of bleeding	In vitro	[79]
				Inflamation	Decreased COX, 5-LOX and sPLA2	Increase the risk of bleeding	Docking	[79]
Zingiber officinale Roscoe	Ginger	Zingiberaceae	NA	Platelet activation	Decreased TXA2; PAF inhibition	Increase the risk of bleeding	Review	[1,32,33]

Note: All plant species contained in the review by Leite et al., 2016 were included in this table and their scientific names are underlined to facilitate their identification; CAM= Complementary and Alternative Medicine; NA=Not applicable due to study design (literature review of in silico studies; ND= Not described.

there are two main reasons: the lack of training of professionals in herbal medicine and the lack of information about herb-drug interactions [3,12].

The review published in 2016 identified 58 different plant species that had the potential to interact with warfarin. The studies included in that review were mostly superficial and did not address mechanistic issues about herb-warfarin interactions. Furthermore, most of the species presented there had the potential to increase the effect of warfarin, as they act on platelets, coagulation, and inflammation, or even modify the action of this anticoagulant. Still, the five most commonly mentioned medicinal plants were, respectively, ginseng, garlic, ginkgo, St. John's Wort, and ginger [1].

Several literature reviews involving herb-warfarin interactions were found. Some were focused on the herbal medicines most used in Oriental Traditional Medicine, others were focused on pharmacokinetic interactions, and still others assessed the quality of the herb-drug interactions evidence. In this scenario, our article groups all this information and present 114 plant species that have already shown some evidence of interaction with warfarin. The type of study involved in determining each interaction is also highlighted to critically help assess the clinical relevance of these interactions. The management of patients using warfarin is multifactorial and the information presented here can contribute to herb-warfarin interaction field as well as direct new studies on this topic.

This review, thus, gathers and summarizes information on potential interactions of herbal medicines with warfarin, as well as brings additional information regarding the targets of the interaction and type of study carried out to critically support the assessment of the real clinical

implications of herb-warfarin interactions. The main outcome of the interactions found is the increased anticoagulant effect, which leads to an increased risk of bleeding (Table 1), a fact that corroborates other literature reviews [1,82]. Some examples are garlic, ginger, and ginkgo, as presented in the previous review, but also flaxseed, horse chestnut, and saffron, which were not presented there (Table 1). The reduction of the anticoagulant effect is also a possible outcome, but it was less mentioned (Table 1). Some examples are green tea psyllium and soybean (Table 1).

Also, due to the chemical complexity of the herbal medicines, there is the possibility that the same plant has the potential to increase and decrease the effect of warfarin, as some of its substances may have anticoagulant activity, while others a pro-coagulant effect. Examples include *Aloe vera*, *Camellia sinensis*, *Glycine max*, and *Panax ginseng* (Table 1 and Graphical abstract). Aloe has the potential to decrease warfarin intestinal absorption [14]; however, there is a case report in which this plant increased the risk of bleeding [32]. Soybean, in turn, may increase the effect of warfarin due to CYP inhibition [33], but may also reduce its effect due to changes in P-gp/OATP transporters and due to high vitamin K content [10,14]. There were also two plant species that showed variable activity according to the dose or time of use: *Mentha pulegium* [59] and *Pogostemon cablin* [69].

These herb-warfarin interactions can occur either to the change in the drug's action by modifying its concentration (pharmacokinetics) or by competition for its target (pharmacodynamics), or by changes in the coagulation pathway directly or indirectly (platelet activation pathways and inflammation) (Graphical abstract). Unfortunately, as noted in the previous review [1], studies that directly assessed the mechanism involved in these interactions are still scarce. For this reason, as in the previous review [1], secondary data were included, with a view to encompassing a greater number of herbal medicines and directing more in-depth studies with these species.

In this sense, the description of the source of evidence aims to assist in the critical evaluation of the quality of evidence of herb-warfarin interactions. It is important to add that data from primary sources includes animal studies, in vitro studies, case reports and even theories or speculations, as is the case of species rich in coumarins, such as chamomile and guaco [12] and this information should be used considering the limitations of each type of study. Also, in the context of herbal medicine, unravel the chemical substances and molecular targets involved in interactions is very difficult due to the chemical complexity of medicinal plants and the complexity of haemostasis, which involves the relationship between the processes of blood coagulation and platelet activation and inflammation, among others. It is believed, however, that this branch of science will evolve considerably with the development of computational techniques, as could already be seen in one study with *P. ginseng* [62].

4.1. Coagulation

Blood coagulation is a process that involves the sequential proteolytic activation of proenzymes by plasma proteases, resulting in the formation of thrombin, which breaks the fibrinogen molecule into fibrin monomers, which polymerize to form the clot. This process is didactically divided into extrinsic and intrinsic pathways, which respond to tissue factor (TF) release and vascular injury, respectively. The fibrinolysis process counterbalances this process through clot degradation, seeking balance (Graphical abstract) [1,83,84].

All reactions involving the activation of these coagulation factors are potential targets to increase or reduce the blood coagulation process; that is, they are also targets for interaction with warfarin. There are assays for measuring these clotting factors, but the tests most commonly used in the clinic to assess blood clotting are the Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT), which respectively assess the extrinsic and intrinsic pathways of blood coagulation. More recently, the Thrombin Generation Test (TGT) has been applied in research with this objective, being a more robust and complete option for evaluating blood coagulation [12,13,84].

Most of the plants presented in this review that have an effect on blood coagulation were studied using PT and aPTT tests (Table 1). Some were also studied for their effect on bleeding time (BT), clotting time (CT), and thrombin time (TT) (Table 1), which are less specific screening tests for the coagulation profile. TGT was also used and corroborated the results of PT and aPTT in the species *Mentha crispa* and *Mikania laevigata* (Table 1) [12,13]. These plants prolonged the clotting time in these different coagulometric tests, demonstrating anticoagulant potential. However, it is not possible to determine which step of the coagulation cascade is being inhibited.

P. ginseng, in contrast, has its effect on blood coagulation best elucidated. It was able to activate factors II, VII, and protein Z in rats [61], revealing potential pro-coagulant effect. However, it also inhibited factor Xa in vitro and by molecular docking [62], resulting in anticoagulant activity, which as discussed earlier can happen due to the wide variety of substances present in ginseng. To determine, then, the real effect of this plant on blood clotting, a clinical trial is needed.

4.2. Platelet activation

Platelet activation is another complex process that is part of hemostasis, which involves four distinct processes: adhesion (deposition of platelets in the subendothelial matrix), aggregation (platelet cohesion), secretion (release of proteins from platelet granules), and procoagulant activity (intensification thrombin generation). Platelet activation is induced by collagen, thrombin, ADP, TXA2, and epinephrine, leading to the activation of platelet adhesion receptors, mainly the αIIbβ3 integrin, which mediate platelet adhesion and aggregation. Platelets release tissue factor, which in turn will activate the coagulation cascade, forming more thrombin, which will activate more platelets via two G protein-coupled receptors on human platelets, PAR-1 and PAR-4 (Graphical abstract) [85,86].

Due to this relationship between platelet activation and blood coagulation, the increase or decrease in platelet activity in a human, in vivo, will also affect blood coagulation. The target of herbal medicines in platelet activation is better studied. Some plants are traditionally known for having substances that inhibit the platelet aggregation factor (PAF), such as *Allium sativum*, *Ginkgo biloba*, and *Zengiber officinale*. For this reason, these plants should even be avoided before surgical procedures [1,14,32,33,37].

Other mechanisms have also been described: *Angelica sinensis* reduces the release of ADP and serotonin from platelets [14]; *Astilbe chinensis* and *Morus alba* [36,60] reduce the binding of fibrinogen to integrin; *Linum usitassinum* [32] seems to promote changes in the composition of the platelet membrane; and others such as *Allium cepa* and *Citrus paradisi* act at the interface between platelet activation and inflammation by reducing TXA2 synthesis [1,31] (Table 1).

4.3. Inflammation

Inflammation is a natural response in the body that takes place in response to disorders such as infection, injury, or trauma. Its aim is to eliminate the cause of that disorder, dead cells, and damaged tissue, as well as begin repairing them. This process is well known to be related to blood clotting by several mechanisms. The most traditional connection that refers to this inflammation/coagulation relationship is via platelets: activation of the arachidonic acid pathway leads to the production of TXA2 which stimulates platelet aggregation, which in turn leads to blood clotting. A classic example of this effect is acetylsalicylic acid, a drug used as an anti-inflammatory and as an anti-aggregant, in low doses. However, there are other interfaces between inflammation and blood coagulation in the body, such as TF: Some inflammatory cytokines, such as tumor necrosis factor-α or interleukins, strongly induce expression of TF, which leads to activation of the coagulation cascade

(Graphical abstract) [83,87,88].

In this context, it is expected that herbal medicines that act on inflammation may also impact the blood clotting process. Some examples found in this review include *Camellia sinensis* and *Curcuma longa*, which reduce the activation of the arachidonic acid pathway; *Serenoa repens*, which reduces the activity of COX and other products of the arachidonic acid pathway; and *Withania somnifera*, which reduces COX, 5-lipoxygenase (5-LOX), and sPLA2 (Table 1). However, the impact of this inflammation/coagulation relationship for interactions with anticoagulants needs to be further studied, as there is a range of herbal medicines with expressive and proven anti-inflammatory activity that might or might not interact with warfarin.

4.4. Warfarin pharmacokinetics and pharmacodynamics

Pharmacokinetics and pharmacodynamics are related to the action of drugs on the body. Pharmacokinetics refers to the path that the drug takes in the body, encompassing the stages of absorption, distribution, metabolism, and excretion. Pharmacodynamics, in turn, refers to the interaction of the drug with its receptor, producing the therapeutic effect [89]. Warfarin has pharmacokinetic characteristics that favors the occurrence of interactions such as high bioavailability, high plasma protein binding rate, and metabolization by cytochrome P450 enzymes. Furthermore, as it is a drug with a low therapeutic index, any change in its concentration can bring a great risk. This is why interactions involving warfarin are so relevant. In this context, warfarin is the drug most involved in interactions with herbal medicines, but, surprisingly, this issue has not been so explored yet [1,5,14,80,90].

As in the previous review [1], interactions with warfarin resulting from enzyme induction or inhibition are the most studied. In this sense, there were 22 references of interaction by inhibition of CYPs that metabolize warfarin (CYP 2C9, 1A2, and 3A4), including plants such as *Cannabis sativa* [91] and *Lycium barbarum* [14,57]. These interactions would slow the metabolism and, consequently, the elimination of warfarin, increasing its effect. Regarding the induction of the metabolism of this anticoagulant, there were 5 references, including plants such as *Hypericum perforatum* and *Panax ginseng* (Table 1) [14,37,38].

However, there were also reports of possible interactions in the other pharmacokinetic steps: *Glycine max* altered P-gp/OATP transporters [10]; *Salvia miltiorrhiza* decreased warfarin binding rate to albumin [37]; and *Aloe vera* and *Medicago sativa* decreased intestinal warfarin absorption and/or increased renal warfarin clearance (Table 1) [14].

Regarding its pharmacodynamics, warfarin acts by inhibiting vitamin K epoxide reductase (VKOR). It interferes with the activation of some clotting factors by blocking the vitamin K oxidation-reduction cycle needed for the carboxylation of these factors [1,80]. Thus, plants rich in vitamin K, such as *Peumus boldus* [33] and *Verbena officinalis* [14], would antagonize this anticoagulant. In contrast, herbal medicines that have substances capable of binding to the same sites as warfarin would increase its effect. One possibility in this regard is plants rich in coumarin, such as *Mikania laevigata,* as warfarin was developed from dicoumarol, a dimeric coumarin. However, so far, this is based on speculation, and there are no in vivo studies [12].

Finally, it should be noted, in relation to the previous review, we started to find articles that studied the anticoagulant potential of medicinal plants through *in silico* studies, such as molecular docking [62], and these articles tend to appear more and more. This scientific evolution is very important as it can facilitate the study of interactions. With regard to hemostasis, all enzymes involved in this complex control (Graphical abstract) could be used as targets for *in silico* studies, enabling a more complete view of the effect of substances in this process and their impact on warfarin pharmacotherapy, for example, showing directions for further studies that effectively prove the action. Yet, these studies can also help in the discovery and development of drug candidates that act on hemostasis, such as antithrombotics. In this sense, innovations also appeared in the last 5 years, such as the development of materials for implants that come into contact with blood, cardiac patches, and grafts [25].

5. Final considerations

The term herb-drug interactions was introduced as a Medical Subject Headings (MeSH) term only in 2004, which justifies the lack of information on the subject. However, this theme is extremely relevant for patient care in that the clinical impact of these interactions can cause adverse events and can also impair the effectiveness of the patient's pharmacotherapy [5,7,90]. This review brought 114 plant species that have the potential to modify the warfarin effect. Most of them presented can increase the risk of bleeding through various mechanisms and, per se, can also be great candidates for the development of antithrombotics with a safer profile. Overall, the herbal medicines presented in this review should be used with caution in patients taking warfarin, as there is evidence of a potential interaction.

Regardless of the opinion of health professionals about the use of medicinal plants, patients use them, often indiscriminately and without realizing that they are also medicines. Therefore, it is very important to encourage the training of these professionals in the area, aiming to promote the rational use of medicinal plants and improving the quality and safety of pharmacological treatments [1,3,12]. In addition, it is essential that professionals critically assess the information available during the clinical management of herb-drug interactions, taking into account the types of studies carried out and their limitations.

In this sense, it is known that the clinical management of interactions is effective [5,12,90]. In other words, it is possible that the use of plants in conjunction with warfarin is safe, but for that, it is necessary to advance in this theme. Also, as the effect of warfarin can be monitored via international normalized ratio (INR), it is possible to use the dose adjustment of this drug as a tool for the clinical management of these interactions [2,3]. It is always extremely important to consider the particularities of each patient and be cautious in this management, given the limitations of pharmacotherapy with warfarin.

In this sense, it is essential that there is an awareness of health professionals to seek training in the area of interaction with herbal medicines and to develop an appropriate approach to deal with patients using herbal medicines, in order to combat their unattended use [1,7,92]. Regarding the information available on herb-drug interactions, it is clear that it needs to be deepened. Therefore, it is important that research be stimulated to generate this type of content to support patient care, whether looking for ways to apply the results of in vitro and animal studies in clinical reality or through alternatives to study herb-drug interactions.

CRediT authorship contribution statement

Paula Mendonça Leite: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Maria das Graças Carvalho:** Conceptualization, Methodology, Resources, Writing – original draft, Supervision. **Maria Auxiliadora Parreiras Martins:** Conceptualization, Methodology, Resources, Writing – original draft, Supervision. **Rachel Oliveira Castilho:** Conceptualization, Methodology, Resources, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2021.112103.

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