Drug–Food Interactions of DOACs

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In recent years direct oral anticoagulants (DOACs) have become the anticoagulant treatment of choice. DOACs were initially considered drugs with no significant food interactions; however, clinical observations from daily practice have proved otherwise as interactions with food ingredients have been reported. Food, dietary supplements or herbs may contain substances that, when administered concomitantly with DOACs, can potentially affect the plasma concentration of the drugs.

resveratrol supplementation dabigatran rivaroxaban apixaban edoxaban betrixaban dietary supplements food interaction treatment

1. Introduction

For almost 60 years, vitamin K antagonists (VKAs) were the mainstay of anticoagulation therapy [1]. In 2008, a new class of drugs was introduced in the markets of the European Union and the United States, which was a promising alternative to VKAs in the prevention of embolic complications in non-valvular AF, as well as in the treatment of patients with deep vein thrombosis and pulmonary embolism [2]. These were new-generation oral anticoagulants, originally referred to as new/novel oral anticoagulants (NOACs) and now as direct oral anticoagulants (DOACs) [3]. They act as direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban and betrixaban) or direct thrombin inhibitors (dabigatran) [4][5]. Their anticoagulant effect is more predictable and stable (i.e., less dependent on interactions with food, herbal supplements and other drugs) compared to warfarin and acenocoumarol [6]. The use of DOACs does not require individual dose adjustment or routine monitoring of blood coagulation parameters, such as the international normalized ratio (INR), activated partial thromboplastin time (APTT) and thrombin time [4]. Using VKA therapy, the therapeutic INR range of 2.0– 3.0 is recommended in the prevention of embolic complications in non-valvular AF, in the treatment of deep vein thrombosis and pulmonary embolism. It is recommended that time in therapeutic range (TTR) be >70% during VKA therapy, which in the context of significant dietary interactions and individual pharmacokinetic profiles mandates frequent INR control. Therefore, thecost-effectiveness and safety of long-term VKA treatment are considerably lower [4]. However, contrary to common belief, some pharmacokinetic variations secondary to interactions with food, herbal supplements and other drugs should still be considered in patients treated with DOACs [7][8].

2. Bioavailability and Metabolism of DOACs

DOAC bioavailability is affected by the renal excretion of drugs, gastrointestinal and renal re-secretion by ABC transporters as well as drug metabolism by cytochrome P450 (CYP) enzymes [9]. P-glycoprotein (P-gp/ABCB1/multidrug resistance 1 (MDR1)) and breast cancer resistance protein (BCRP/ABCG2/ABCP) belong to the family of ABC transporters that protect cells from toxic effects of substances by removing them against the concentration gradient through the cell membrane, consuming energy from ATP hydrolysis [10]. P-gp and BCRP are present on the apical membrane of cells in several normal human organs (liver, kidneys, adrenal gland) and tissue junctions (blood–brain barrier, intestine, placenta, blood–testis and blood–ovarian barriers) [10]. They protect the human organism against the detrimental effects of xenobiotics, but by the same token, they take part in drug–drug and drug–food interactions [11]. In addition, food and drugs affect the activity of cytochrome P450 enzymes involved in drug metabolism, also contributing to important interactions [12]. In fact, DOACs, except for dabigatran and betrixaban, are mainly metabolized by the CYP3A4 isoform, which is present both in the gut and the liver [13]. Concomitant use of DOACs with other drugs, certain food or herbs may affect the activity of drug transporters and metabolizing enzymes, which may result in pharmacokinetic interactions leading to low efficacy or unexpected toxicities [13]. The absorption and metabolism of DOACs are presented in **Figure 1**.

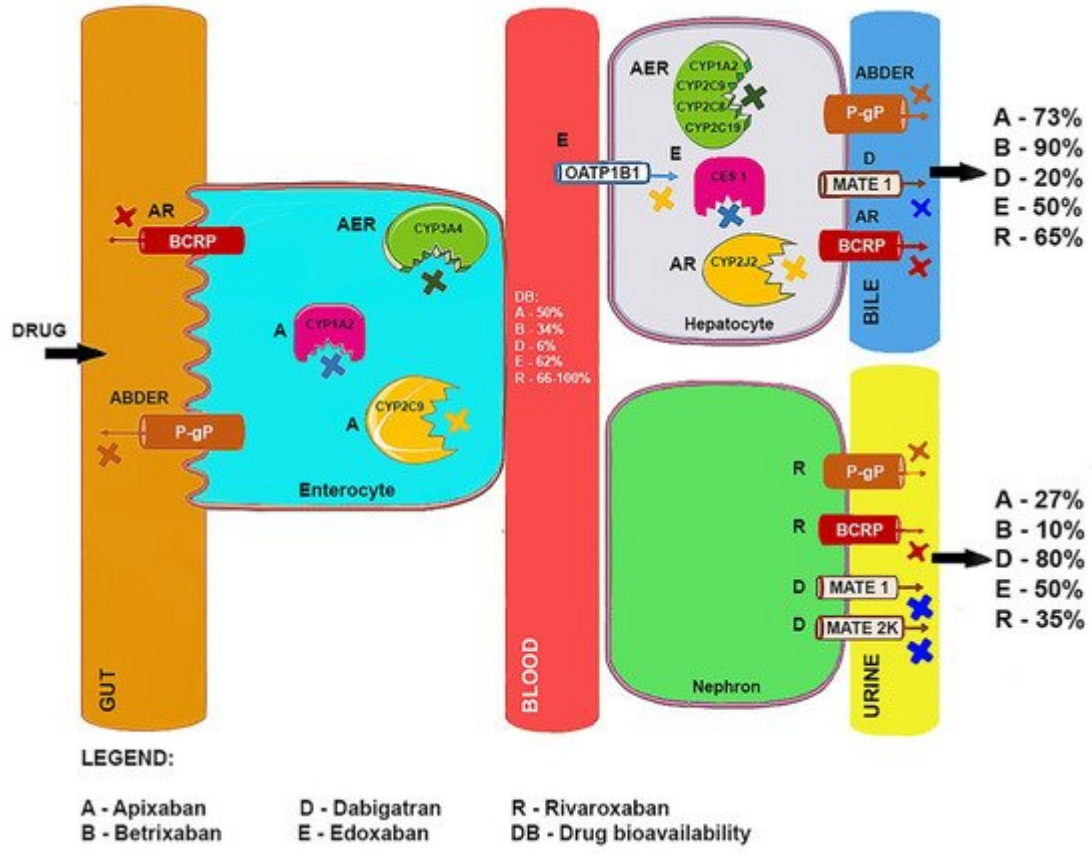

Figure 1. The absorption and metabolism of DOACs [9][13][14][15][16][17][18][19].

3. Use of DOACs with Proton Pump Inhibitors and Activated Charcoal

In a 2018 study on DOACs, the authors emphasize that long-term therapy may require more effective stomach protection through the use of proton pump inhibitors (PPIs) [20]. PPIs have also been shown to be useful in alleviating indigestion associated with dabigatran [21].

In the event of DOAC overdose, the use of activated charcoal may be considered. In vitro data indicate that dabigatran can be effectively absorbed by activated carbon. Importantly, the administration of activated charcoal is recommended in the event of bleeding if no more than 2 h have passed since the last dose [22].

4. DOAC Treatment in Patients after Gastrointestinal Surgery

Patients after gastrointestinal surgery treated with DOACs should be monitored more carefully. The therapy could be continued provided that the measured peak plasma and trough concentrations correspond to values expected in the general population [23]. It is recommended to avoid rivaroxaban treatment in patients undergoing gastrectomy, yet patients who have sustained major distal bowel resection could be treated with this agent. Dabigatran should be avoided in patients who underwent gastrectomy or major proximal or distal intestinal resections, according to isolated reports [24].

5. Diet with DOACs

Some authors suggest that intermittent fasting can be a method of prevention of cardiovascular diseases [25]. This suggestion is based on a slight decrease in LDLcholesterol concentration observed after fasting, but so far it has not been confirmed in direct clinical trials. Moreover, from the point of view of pharmacokinetics, prolonged fasting in patients on active pharmacological treatment may be dangerous due to the possible changes in drug absorption leading to ineffective therapy and therefore potentially to myocardial infarction, stroke and other thrombotic events.

Studies on interactions between apixaban, edoxaban, dabigatran and individual macronutrients showed that the presence of proteins, fats and carbohydrates did not significantly affect the bioavailability of these drugs [26][27][28]. However, the results of an in vitro study by Raiola et al. showed that the presence of insoluble and soluble fiber as well as cellulose may cause a decrease in the bioavailability of dabigatran, rivaroxaban and apixaban. The presence of a high amount of insoluble and soluble dietary fiber significantly decreased DOAC bioavailability. However, a low or moderate amount of fiber did not have a significant effect on the bioavailability of DOACs, i.e., when they were a component of a balanced meal containing all the macronutrients. The study results suggest that it may be necessary to maintain a time interval between taking DOACs and a meal containing a high amount of cellulose and inulin. The authors of the study emphasize that further in vivo research is needed to evaluate the effect of dietary fiber on the bioavailability of anticoagulants [29].

6. DOAC Interaction with Dietary Supplements

When choosing these products, patients often follow the opinion of pharmacists, who do not always have sufficient knowledge about their indications [30]. Dietary supplements are used in the treatment of cardiovascular diseases such as hypertension, hyperlipidemia, coronary artery disease, stroke and peripheral arterial disease. In addition, they delay the aging process and reduce the risk of dementia [31][32][33]. However, their use alongside DOAC therapy carries the risk of bleeding or a reduction in the therapeutic effect (**Table 1**). Some of these agents have antiplatelet effects, which in conjunction with DOACs can potentially significantly increase the risk of bleeding, as is obviously the case when combining anti-platelet drugs with DOACs [34].

Table 1. Potential effect of food ingredients on DOACs [9][19][35][36][37][38][39][40][41][42][43][44][45].

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
Alpha-lipoic acid		Exhibits antiplatelet activity	Potentially increases the risk of bleeding when used concomitantly with DOACs
Apigenin *	*M. chamomilla* (*Camomile*) *M. officinalis* (*Lemon balm*) *P. emblica* (*Emblic myrobalan*) *S. costus* (*Costus*)	Inhibition of cytochrome P450 (1A2, 2C9, 2C19, 3A4), P-gp and BCRP Exhibits antiplatelet activity	Potentially increases plasma concentration of all DOACs Potentially increases the risk of bleeding when used concomitantly with DOACs
α-Asarone	*A. calamus* (*Sweet flag*) *A. gramineus* (*Japanese sweet flag*)	Inhibition of cytochrome P450 (1A1, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1) and P-gp	Potentially increases plasma concentration of all DOACs
β-Asarone	*A. calamus* (*Sweet flag*) *A. gramineus* (*Japanese sweet flag*) *R. acori*	Inhibition of CYP3A4 and P-gp	Potentially increases plasma concentration of all DOACs
Avenanthramide (A, B, C) *	*A. sativa* (*Oat*)	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
Bacoside (A, B) *	*B. monnieri*(*Water hyssop*)	Inhibition of cytochrome P450 (1A2, 3A4, 2C9, 2C19)	Potentially increases plasma concentration of rivaroxaban,

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
			apixaban and edoxaban
Berberine *	*C. chinensis* (*Chinese goldthread*) *C. japonica* (*Camellia*)	Inhibition of cytochrome P450 (1A2, 3A4, 2C9, 2D6), P-gp and BCRP	Potentially increases plasma concentration of all DOACs
Bilobalide *	*G. biloba* (*Ginko*)	Inhibition of cytochrome P450 (1A1, 1A2, 3A4, 2B6, 2C9, 2E1) and P-gp	Potentially increases plasma concentration of all DOACs
Biochanin A *	*T. pratense* (*Red clover*)	Inhibition of CYP3A4, P-gp and BCRP Exhibits antiplatelet activity. May enhance effects of anticoagulant	Potentially increases plasma concentration of all DOACs Potentially increases the risk of bleeding when used concomitantly with DOACs
Caffein *	*C. arabica* (*Arabian coffee*) *I. paraguariensis* (*Yerba mate*) *P. cupana* (*Guaraná*) *T. cacao* (*Cacao tree*) *C. sinensis* (*Chinese liver fluke*)	Inhibition of cytochrome P450 (1A2, 3A4) and BCRP	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban
Capsaicin *	*Capsicum* (*Chili peppers*)	Induction of CYP3A4 and inhibition of P-gp	Potentially increases plasma concentration of dabigatran and betrixaban
Carbolines (Harmine) *	*L. meyenii* (*Maca*) *M. pruriens* (*Velvet bean*) *P. harmala* (*Wild rue*)	Inhibition of cytochrome P450 (1A1,1A2, 2C9, 2C19, 2D6, 2E1) and BCRP	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban
Casticin *	*V. agnus-castus* (*Chaste tree*)	Inhibition of cytochrome P450 (3A4, 2C9)	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
Catechin *	*C. rotundus* (*Coco-grass*) *L. bicolor* (*Shrub lespedeza*) *M. chamomilla* (*Camomile*) *T. cacao* (*Cacao tree*)	Inhibition of cytochrome P450 (1A2, 3A4, 2C9) and P-gp	Potentially increases plasma concentration of all DOACs
Chebulagic acid *	*T. chebula* (*Chebulic myrobalan*) *P. emblica* (*Emblic myrobalan*)	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
Chicoric acid, Alkylamides *	*G. Echinacea* (*nine known species*)	Inhibition of CYP3A4	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban
Cinnamaldehyde *	*C. wilsonii*	Inhibition of cytochrome P450 (1A2, 2E1) and P-gp	Potentially increases plasma concentration of all DOACs
Coniferyl ferulate *	*A. sinensis*(*Dong quai*)	Inhibition of cytochrome P450 (3A4, 2D6) and P-gp	Potentially increases plasma concentration of all DOACs
Coraria lactone	*Alismaorientalis* (*Alismataceae*)	Induction of P-gp	Potentially decreases plasma concentration of all DOACs
Coumarin *	*A. hippocastanum* (*Horse chestnut*) *Cassia cinnamon* (*Cinnamon*)	Exhibits antiplatelet activity	Potentially increases the risk of bleeding when used concomitantly with DOACs
Crocin *	*C. sativus* (*Saffron*)	Inhibition of cytochrome P450 (3A4, 3A5, 3A7,2B6) and P-gp	Potentially increases plasma concentration of all DOACs
Curcumin *	*C. longa* (*Turmeric*)	Inhibition of cytochrome P450 (1A2, 3A4, 2B6, 2C9, 2D6) and P-gp, induction/inhibition of BCRP Exhibits antiplatelet	Potentially increases plasma concentration of all DOACs Potentially increases the risk of bleeding when

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
		activity. May enhance effects of anticoagulant.	used concomitantly with DOACs
Decursin *	*A. gigas* (*Korean angelica*)	Inhibition of cytochrome P450 (1A1, 1A2) and P-gp	Potentially increases plasma concentration of all DOACs
Dehydroepiandrosterone *	*Soybean* (*Glycine max*)	Inhibition of CYP3A4	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban
Delphinidin *	*V. uliginosum L.* (*Bog bilberry*)	Inhibition of cytochrome P450 (3A4, 2B6, 2C9), and BCRP	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban
Ellagic acid *	*T. chebula* (*Chebulic myrobalan*) *P. emblica* (*Emblic myrobalan*)	Inhibition of BCRP	Potentially increases plasma concentration of rivaroxaban and apixaban
Ent-kaurane *	*C. tonkinensis*	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
Ephedrine *	*Angelica sinensis*(*Apiaceae*)	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
Epicatechin gallate (ECG) * Epigallocatechin-3-gallate (EGCG) *	*C. sinensis* (*Chinese liver fluke*)	Inhibition of cytochrome P450 (1A1, 1A2, 3A4) and P-gp	Potentially increases plasma concentration of all DOACs
Eucalyptus oil	*E. globulus* (*Eucalyptus*)	Inhibition of cytochrome P450 (1A2, 2C9, 2C19, 3A4)	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
Feverfew oil	*T. parthenium* *(*Feverfew*)	Inhibition of cytochrome P450 (1A2, 2C9, 2C19, 3A4) Exhibits antiplatelet activity	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban Potentially increases the risk of bleeding when used concomitantly with DOACs
Galantamine *	*G. nivalis* (*Snowdrop*) *G. woronowii* (*Green snowdrop*) *L. radiata* (*Red spider lily*) *N. confusus* (*Lily of Mary*) *P. illyricum*	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
Gallic acid *	*M. pruriens* (*Velvet bean*) *P. emblica* (*Emblic myrobalan*) *T. chebula* (*Chebulic myrobalan*)	Inhibition of CYP3A4 and P-gp	Potentially increases plasma concentration of all DOACs
Gingerol *	*A. melegueta* (*Melegueta pepper*) *Z. officinaleRosc* (*Ginger*)	Inhibition of cytochrome P450 (3A4, 2C9, 2C19) and P-gp Exhibits antiplatelet activity	Potentially increases plasma concentration of all DOACs Potentially increases the risk of bleeding when used concomitantly with DOACs
Ginkgolide A, B *	*G. biloba* (*Ginkgo*)	Inhibition of cytochrome P450 (3A4, 2C9) and induction of P-gp Exhibits antiplatelet activity	Potentially decreases plasma concentration of dabigatran and betrixaban Potentially increases the risk of bleeding when used concomitantly with DOACs
Ginsenoside Rb, Rd *	*P. ginseng* (*Ginseng*)	Inhibition of cytochrome P450 (3A4, 2C9), BCRP	Potentially increases plasma concentration of rivaroxaban,

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
		Exhibits antiplatelet activity	apixaban and edoxaban Potentially increases the risk of bleeding when used concomitantly with DOACs
Glabridin *	*G. glabra* (*Licorice*)	Inhibition of CYP3A4 and P-gp	Potentially increases plasma concentration of all DOACs
Grapefruit juice	*C. paradisi* (*Grapefruit*)	Inhibition of CYP3A4 and P-gp	Potentially increases plasma concentration of all DOACs
Guggulsterone *	*Guggul* (*Commiphoramukul*)	Induction CYP3A4 and inhibition of P-gp	Potentially increases plasma concentration of dabigatran and betrixaban
Honokiol *	*P. kaempferi* (*Pinaceae*)	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
Hydrastine *	*Hydrastis canadensis* (*Goldenseal*)	Inhibition of CYP3A4	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban
Hyperforin, hypericin *	*H. perforatum* (*St. John's wort*)	Induction of cytochrome P450 (1A2, 2C9, 3A4) and P-gp	Decreases plasma concentration of all DOACs Concomitant use with dabigatran and rivaroxaban should be avoided. Concomitant administration with edoxaban and apixaban should be used with caution (according to EHRA)

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
1,2,3,4,6-Penta-*O*-galloyl--d-glucose *	*T. chebula* (*Chebulic myrobalan*)	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
E-Harpagoside *	*S. buergeriana* (*Buerger's Figwort*)	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
Kavalactones *	*Piper methysticum* (*Kava*)	Inhibition of cytochrome P450 (1A2, 2C9, 3A4) and induction of P-gp	Potentially decreases plasma concentration of dabigatran and betrixaban
Lime extract	*C.aurantifolia* (*Lime*)	Inhibition of CYP3A4	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban
Luteolin *	*L. bicolor* (*Shrub raspedeza*) *M. chamomilla* (*Camomile*) *M. officinalis* (*Lemon balm*) *P. emblica* (*Emblic myrobalan*) *R. officinalis* (*Rosemary*)	Inhibition of cytochrome P450 (1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1) and P-gp Exhibits antiplatelet activity	Potentially increases plasma concentration of all DOACs Potentially increases the risk of bleeding when used concomitantly with DOACs
Malvidin 3-galactoside *	*V. angustifolium* (*Wild lowbush blueberry*)	Inhibition of cytochrome P450 (3A4, 2C9), BCRP, P-gp	Potentially increases plasma concentration of all DOACs
Malvidin 3-glucoside *	*V. angustifolium* (*Wild lowbush blueberry*) *V. uliginosum L.* (*Bog bilberry*)	Inhibition of cytochrome P450 (3A4, 2C9), BCRP, P-gp	Potentially increases plasma concentration of all DOACs
Mangiferin *	*M. indica* (*Mango*)	Inhibition of cytochrome P450 (1A1,1A2, 3A4, 2B6, 2C8, 2D6) and P-gp	Potentially increases plasma concentration of all DOACs
Myricetin *	*M. peregrina* (*Ben tree*) *R. nigrum* (*Blackcurrant*)	Inhibition of cytochrome P450	Potentially increases plasma

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
		(1A2, 3A4, 2D6), BCRP and P-gp	concentration of all DOACs
Naringenin	*L. bicolor* (*Shrub lespedeza*) *M. lucida* (*Brimstone tree*)	Inhibition of cytochrome P450 (3A4, 2C9, 2C19, 2E1), P-gp and BCRP	Potentially increases plasma concentration of all DOACs
Nobiletin *	*C. reticulata* (*Mandarin*)	Inhibition of CYP3A4, BCRP and P-gp	Potentially increases plasma concentration of all DOACs
Oleanolic acid *	*M. lucida* (*Brimstone tree*) *R. officinalis* (*Rosemary*)	Inhibition of cytochrome P450 (1A2, 3A4), BCRP and P-gp	Potentially increases plasma concentration of all DOACs
Omega-3 polyunsaturated fatty AIDS (n-3 PUFA)	*Fish oil*	Exhibits antiplatelet activity	Potentially increases the risk of bleeding when used concomitantly with DOACs
Paeoniflorin *	*Paeonia alba* (*Paeoniaceae*)	Induction of P-gp	Potentially decreases plasma concentration of all DOACs
p-Synephrine *	*C. aurantium* (*Bitter orange*)	Inhibition of CYP3A4 and P-gp	Potentially increases plasma concentration of all DOACs
Paeonol *	*P. lactiflora* (*Chinese peony*)	Inhibition of BCRP	Potentially increases plasma concentration of rivaroxaban and apixaban
Palmatine	*C. chinensis* (*Chinese goldthread*) *C. speciosa*	Induction of CYP3A4 and P-gp	Potentially decreases plasma concentration of all DOACs
Phellamurin	*Phellodendronwilsonii*(*Rutaceae*)	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
Phyllanthin *	*P. emblica* (*emblic myrobalan*)	Inhibition of CYP3A4 and P-gp	Potentially increases plasma concentration of all DOACs
Piperine *	*P. nigrum* (*Black pepper*) *P. longum* (*Long pepper*)	Inhibition of cytochrome P450 (3A4, 2C9, 2E1), P-gp and BCRP	Potentially increases plasma concentration of all DOACs
Polyphenols *	*Theaceae* (*Green tea leaf*)	Short-term inhibition and long-term induction of CYP3A4, induction of P-gp Exhibits antiplatelet activity	Potentially decreases plasma concentration of all DOACs Potentially increases the risk of bleeding when used concomitantly with DOACs
Prunus avium extract	*P. avium* (*Wild cherry*)	Inhibition of CYP3A4	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban
Pyranocoumarins	*P. praeruptorum* (*Ningqianhu*)	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
Quercetin *	*A. melegueta* (*Melegueta pepper*) *C. sativus* (*Saffron*) *C. rotundus* (*Coco-grass*) *H. perforatum* (*St. John's wort*) *I. paraguariensis* (*Yerba mate*) *L. meyenii* (*Maca*) *M. lucida* (*Brimstone tree*) *P. emblica* (*Emblic myrobalan*) *R. nigrum* (*Blackcurrant*) *S. costus* (*Costus*) *V. uliginosum L.* (*Bog bilberry*)	Inhibition of cytochrome P450 (1A1, 1A2, 3A4, 2C8, 2C9, 2C19, 2D6) and P-gp, induction of BCRP Exhibits antiplatelet activity	Potentially increases plasma concentration of dabigatran, edoxaban and betrixaban Potentially increases the risk of bleeding when used concomitantly with DOACs
Quercetin-3-*O*--Dglucuronide	*P. pterocarpum* (*Copperpod*)	Inhibition of CYP3A4 and P-gp	Potentially increases plasma concentration of all DOACs

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
Resveratrol *	*V. vinifera* (*Grape*)	Inhibition of cytochrome P450 (1A1, 1A2, 3A4, 2C8, 2C9, 2C19, 2D6) and P-gp, induction of BCRP	Potentially increases plasma concentration of dabigatran, edoxaban and betrixaban
Rosmarinic acid *	*M. officinalis* (*Lemon balm*) *M. spicata* (*Spearmint*) *R. officinalis* (*Rosemary*)	Inhibition of cytochrome P450 (3A4, 2C9, 2C19, 2D6, 2E1), P-gp and BCRP	Potentially increases plasma concentration of all DOACs
Rutin *	*H. perforatum* (*St. John's wort*) *L. bicolor* (*Shrub laspedeza*) *M. chamomilla* (*Camomile*) *M. flexuosa* (*Moriche palm*) *M. lucida* (*Brimstone tree*) *M. peregrina* (*Ben tree*) *V. uliginosum L.* (*Bog bilberry*)	Inhibition of CYP3A4, P-gp and BCRP Exhibits antiplatelet activity	Potentially increases plasma concentration of all DOACs Potentially increases the risk of bleeding when used concomitantly with DOACs
Safranal *	*C. sativus* (*Saffron*)	Inhibition of P-gp and BCRP	Potentially increases plasma concentration of all DOACs
Salidroside *	*R. rosea* (*Golden root*)	Inhibition of CYP3A4 and P-gp	Potentially increases plasma concentration of all DOACs
S-allyl-l-cysteine sulphoxides (alliin) *	*A. sativum* (*Garlic*)	Induction of P-gp and BCRP Exhibits antiplatelet activity	Potentially decreases plasma concentration of all DOACs Potentially increases the risk of bleeding when used concomitantly with DOACs
Salvianolic acid *	*M. spicata* (*Spearmint*) *S. miltiorrhiza* (*Danshen*)	Inhibition of cytochrome P450 (1A2, 3A4) and P-gp, induction of BCRP	Potentially increases plasma concentration of dabigatran, edoxaban and betrixaban

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
Schisandrin B *	*S. chinensis* (*Magnolia vine*)	Inhibition of cytochrome P450 (3A4, 3A5) and P-gp	Potentially increases plasma concentration of all DOACs
Silymarin *	*Silybum marianum* (*Asteraceae*)	Inhibition of CYP3A4 and P-gp	Potentially increases plasma concentration of all DOACs
β-Sitosterol *	*A. lancea* *C. pluricaulis* (*Shankhpushpi*) *M. peregrina* (*Ben tree*) *M. pruriens* (*Velvet bean*)	Inhibition of BCRP	Potentially increases plasma concentration of apixaban and rivaroxaban
Stigmasterol *	*A. lancea*	Inhibition of cytochrome P450 (3A4, 3A5) and P-gp	Potentially increases plasma concentration of all DOACs
Tannic acid *	*T. chebula* (*Chebulic myrobalan*)	Inhibition of cytochrome P450 (1A2, 3A4, 2B6) and P-gp	Potentially increases plasma concentration of all DOACs
Tanshinone I *	*S. miltiorrhiza* (*Danshen*)	Inhibition of P-gp and BCRP	Potentially increases plasma concentration of all DOACs
Tanshinone IIA *	*S. miltiorrhiza* (*Danshen*)	Inhibition of P-gp and BCRP	Potentially increases plasma concentration of all DOACs
Tenacissimoside A	*Marsdeniatenacissima* (*Asclepiadaceae*)	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
Tetrandrine *	*Stephania tetrandra* (*Menispermaceae*)	Inhibition of CYP3A4 and P-gp	Potentially increases plasma concentration of all DOACs
Thymol, γ-terpinene	*C. copticum* (*CarumAjowan*)	Inhibition of CYP3A4	Potentially increases plasma concentration of rivaroxaban,

glycoprotein). Oncologist 2007, 12, 927–941.

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
			apixaban and edoxaban
Timosaponin AIII *	*A. asphodeloides* (*RhizomaAnemarrhenae*)	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
Trigonelline *	*T. foenum-graecum* (*Fenugreek*)	Induction of BCRP	Potentially decreases plasma concentration of apixaban and rivaroxaban
Ursolic acid *	*R. officinalis* (*Rosemary*)	Inhibition of cytochrome P450 (1A2, 3A4, 2C8, 2C9, 2C19, 2D6) and BCRP	Potentially increases plasma concentration of apixaban, rivaroxaban and edoxaban
Valerenic acid *	*V. officinalis* (*Valerian*)	Inhibition of CYP3A4	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban
Vauqueline	*A. sinensis* (*Dong quai*)	Inhibition of P-gp	Potentially increases plasma concentration of all DOACs
Vitamin E		Exhibits antiplatelet activity	Potentially increases the risk of bleeding when used concomitantly with DOACs
	F. multiflora (*Fo-ti-root*)	Inhibition of cytochrome P450 (1A2, 2C9, 2C19, 3A4)	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban
	Lamiaceae (*Scutellaria*)	Inhibition of CYP3A4 and induction of P-gp	Potentially decreases plasma concentration of

23. Bolek, T.; Samoš, M.; Škorňová, I.; Kovář, F.; Galajda, P.; Staško, J.; Kubisz, P.; Mokáň, M. Proton pump inhibition in patients treated with novel antithrombotic drugs: Should we worry about thrombosis? J. Cardiovasc. Pharm. 2018, 72, 71–76.

Substance	Source of Substance	Mechanism of Action	Effect on DOACs
			dabigatran and betrixaban
	Sucralose	Induction of CYP3A4 and P-gp	Potentially decreases plasma concentration of all DOACs
	U. tomentosa (*Cat's claw*)	Inhibition of CYP3A4	Potentially increases plasma concentration of rivaroxaban, apixaban and edoxaban

* Phytochemicals found in food supplements. Abbreviations: BCRP, breast cancer resistance protein; MATE1, multidrug and toxin extrusion protein 1; MATE2K, multidrug and toxin extrusion protein 2K; P-gp, P-glycoprotein; CYP3A4, cytochrome P450 3A4.

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