# Non-vitamin K antagonist oral anticoagulants (NOACs): Is it safe to take them with herbal medicines?

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## Background

Herbal medicines have been widely used for thousands of years and have gained increasing popularity [1]. Many UK patients use herbal medicines, frequently without consulting their conventional healthcare professionals [2]. The use of herbal medicines is complicated by a lack of scientific evidence of their safety and efficacy, together with an under-reporting and underestimation of adverse effects. As herbal medicines are often taken in combination with conventional medicines this increases the potential for pharmacokinetic and/or pharmacodynamic interactions. The clinical implications of any interaction depend on a variety of factors, such as co-administered medicines, the health status of the patient, the composition of the herbal medicine and the dosage regimens used. Herbal medicine–drug interactions have been reported in several studies, but it is sometimes difficult to generalise, as the effects may be ingredient specific. There is, in general, a lack of knowledge among patients and healthcare providers about drug-herb interactions [1].

Currently, four non-vitamin K antagonist oral anticoagulant (NOAC) drugs are available on the UK market as alternatives to warfarin: dabigatran, rivaroxaban, apixaban and edoxaban. Dabigatran is a direct thrombin inhibitor. Rivaroxaban, apixaban and edoxaban are direct factor Xa inhibitors [3].

## Answer

No direct evidence is available regarding the inherent risk of co-administration of herbal medicines with dabigatran, rivaroxaban, apixaban or edoxaban [4]. However the metabolic pathways of these drugs raises concerns for potential interactions with other substances that are inducers or inhibitors of the cytochrome P 450 (CYP450) enzyme system or P-glycoprotein transporters (P-gp) [4,5]. In addition, a number of herbal medicines, or their constituents, might affect antiplatelet activity, or have anticoagulant activity. Some herbal medicines are documented as having caused haemorrhage as a side effect [6]. Concomitant use of substances that affect haemostasis with dabigatran, rivaroxaban, apixaban or edoxaban may increase the risk of bleeding [7]. The clinical significance of any interaction will vary because of interindividual differences in patient factors e.g. age, sex, nutritional status, metabolising capacity [1], liver and kidney function.

**Dabigatran**

Dabigatran is a direct thrombin inhibitor given orally as the mesilate of the prodrug dabigatran etexilate. After oral administration, dabigatran etexilate is rapidly and completely hydrolysed to its active metabolite, dabigatran, by an esterase-catalysed reaction [8]. Dabigatran is not metabolised by CYP450, so has low potential for clinically relevant interactions with medicines metabolised by CYP450 [4].

Dabigatran etexilate is a substrate for P-gp. Concomitant administration of P-gp inhibitors is expected to result in increased dabigatran concentrations. Close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with strong P-gp inhibitors. The manufacturer contraindicates the concomitant use of some strong P-gp inhibitors with dabigatran and advises dosing reduction when it is used with mild to moderate P-gp inhibitors (see SPC) [9].

Concomitant administration of a P-gp inducer is expected to result in decreased dabigatran concentrations and should be avoided [9].

Dabigatran should be used with caution in conditions with an increased risk of bleeding and in situations with concomitant use of medicines affecting haemostasis by inhibition of platelet aggregation. Concomitant treatment with any other anticoagulants, except under specific circumstances (see SPC), is contraindicated [9].

**Rivaroxaban**

Rivaroxaban is a highly selective direct factor Xa inhibitor. It is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Based on in vitro investigations it is also a substrate for P-gp [10]. The manufacturer of rivaroxaban recommends that patients do not receive concomitant systemic treatment with medicines that are strong inhibitors of both CYP3A4 and P-gp. These medicines may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased risk of bleeding. Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp are expected to increase rivaroxaban plasma concentrations to a lesser extent [10].

The manufacturer advises that the concomitant use of rivaroxaban with strong CYP3A4 inducers may lead to reduced rivaroxaban plasma concentrations and should be avoided unless the patient is closely observed for signs and symptoms of thrombosis [10].

Concomitant treatment with any other anticoagulants, except under specific circumstances (see SPC), is contraindicated. Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis [10].

**Apixaban**

Apixaban is a potent, reversible, direct and highly selective active site inhibitor of factor Xa [11]. It is metabolised in the liver mainly via CYP3A4 and CYP3A5 and to a lesser extent by CYP isoenzymes 1A2, 2C8, 2C9, 2C19, and 2J2. Apixaban is a substrate of P-gp. The use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp. No dose adjustment for apixaban is required when co-administered with agents that are not strong inhibitors of both CYP3A4 and P-gp [11].

The concomitant use of apixaban with strong CYP3A4 and P-gp inducers may lead to reduced apixaban plasma concentrations. No dose adjustment for apixaban is required during concomitant therapy with such medicinal products, however in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp, apixaban should be used with caution for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and for the prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE). Apixaban should not be used for the treatment of DVT and PE in patients receiving concomitant systemic treatment with strong inducers of both CYP3A4 and P-gp since efficacy may be compromised [11].

Due to an increased bleeding risk, concomitant use of apixaban with other anticoagulants is contraindicated, except under specific circumstances (see SPC) [11].

**Edoxaban**

Edoxaban is a highly selective, direct and reversible inhibitor of factor Xa [12]. It is not extensively metabolised by CYP3A [13] but it is a substrate for P-gp [12].

Concomitant administration of edoxaban with certain P-gp inhibitors has resulted in increased plasma concentrations of edoxaban in pharmacokinetic studies and may require dose reduction (see SPC). However, the use of edoxaban with other P-gp inhibitors has not been studied [12].

The concomitant use of edoxaban with P-gp inducers may lead to reduced edoxaban plasma concentrations. Edoxaban should be used with caution when co-administered with P-gp inducers [12].

Coadministration of edoxaban with other anticoagulants is contraindicated due to increased risk of bleeding, except under specific circumstances (see SPC). In clinical studies concomitant use of low dose aspirin (≤ 100mg/day), other antiplatelet agents and thienopyridines resulted in approximately a 2-fold increase in major bleeding in comparison with no concomitant use. Edoxaban can be co-administered with low dose aspirin (≤ 100 mg), although there is very limited experience on the use of edoxaban with dual antiplatelet therapy [12]. However, the use of edoxaban in combination with other substances that affect platelet function cannot be assumed to be safe; the manufacturer states that concomitant use of NSAIDs with edoxaban caused an increase in clinically relevant bleeding and is therefore not recommended [12].

While herbal medicines–drug interactions can be explained by pharmacodynamic mechanisms, the vast majority of these potential interactions are of pharmacokinetic origin resulting in changes of absorption and biotransformation of the affected drug [1]. Table 1 summarises the pharmacokinetic / pharmacodynamic activity of some commonly used herbal medicines which may interact with NOACs. Other herbs not included in this list may also interact with NOACs.

**Table 1: The pharmacokinetic / pharmacodynamic activity of some commonly used herbal medicines which may interact with NOACs**.

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| **Black cohosh:**  Black cohosh may interact with drugs that are metabolised by CYP3A4 enzyme [14]. However four small studies in healthy volunteers suggested that black cohosh has a minimal effect on various CYP450 enzymes or P-gp. Further studies are needed to demonstrate the safety of concomitant use of black cohosh and conventional drugs [1]. |
| **Dong quai:**  Prolonged use of dong quai can induce CYP3A4 which may reduce the blood levels and effectiveness of substrate drugs [14].  Dong Quai contains coumarin derivatives and components that may inhibit platelet aggregation. Caution is advised if dong quai and an anticoagulant are taken concomitantly. Monitor for signs and symptoms of excessive bleeding [7]. |
| **Echinacea:**  Conflicting results have been reported regarding the effect of echinacea on CYP activity [1]. Echinacea purpurea root can inhibit CYP1A2 and selectively modulate CYP3A [6]. Echinacea should be used with caution in patients receiving drugs which are substrates of CYP1A2 and CYP3A enzymes[14], particularly those with a narrow therapeutic range [6].  Echinacea purpurea can also inhibit P-gp activity [1]. |

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| **Evening Primrose Oil:**  In *in vitro* experiments, cis-linoleic acid, was found to be a modest inhibitor of the cytochrome P450 isoenzyme CYP2C9 (but this is not expected to result in clinically relevant effects on drug metabolism) and a modest to minor inhibitor of, in order of potency, CYP1A2, CYP2C19, CYP3A4, and CYP2D6 [15].  Evening primrose oil can inhibit platelet aggregation and increase bleeding time. It has been suggested that it may have additive effects with other antiplatelet drugs, but evidence of this is lacking [15]. |
| **Garlic:**  The information is inconsistent, but some sources state that garlic can affect CYP 2C9, 2C19, 2E1, 2A6, 1A2, 2D6, 2E1 and 3A4 [1,14,15]. Additionally, garlic may induce P-gp [14]. Until further data are available, caution is advised if garlic is taken concomitantly with substrates of CYP2E1, CYP3A4 or P-gp [1].  Garlic may have antiplatelet properties. Garlic supplements alone have rarely been associated with bleeding. Although there appear to be no clinical reports of an adverse interaction between garlic and antiplatelet drugs, the potential for an increase in the severity of bleeding if garlic is given with anticoagulants should be considered [15]. Concomitant use of garlic with anticoagulants is not recommended, but if the combination is used, bleeding time and signs and symptoms of excessive bleeding should be monitored [7]. The effect of garlic supplements on CYP isoenzymes and platelet aggregation depends on the dosage and product composition [1].  Regular ingestion of food products containing small amounts of garlic should not pose a problem [7]. |
| **Ginkgo:**  Studies show that ginkgo can inhibit and induce the CYP450 1A2, 2D6 and 3A4 enzymes but data are conflicting [14].Ginkgo inhibits P-gp and can therefore interfere with drugs that are transported by P-gp [14].  Cases of subarachnoid haemorrhage, subdural haematoma, intracerebral haemorrhage, subphrenic haematoma, vitreous haemorrhage and postoperative bleeding have been reported in patients taking ginkgo alone. Since patients taking medications that affect platelet aggregation or blood coagulation may be at increased risk of serious bleeding disorders, concomitant use of ginkgo and anticoagulants should be avoided [7]. |
| **Ginseng, Panax:**  Ginseng inhibited the metabolism of nifedipine, a CYP3A4 substrate in a clinical trial. Other drugs metabolised by CYP3A4 may be similarly affected [7]. Certain ginsenosides can induce CYP3A4 and may increase the clearance of substrate drugs, although the effect in humans may not be clinically significant [14]. As ginseng contains antiplatelet components, excessive bleeding cannot be ruled out [15]. There is a case report of perioperative bleeding due to severe coagulopathy induced by high oral intake of ginseng before surgery [14]. Potential pharmacodynamic interactions have been reported with antiplatelet/anticoagulant drugs [1]. The combination of ginseng with anticoagulants should be avoided if possible [7]. |
| **Ginseng, Siberian:**  Eleutherosides B and E may inhibit CYP2C9 and CYP2E1 which can affect the intracellular concentration of drugs metabolised by these enzymes [14]. Clinical studies have shown that Siberian ginseng may have weak inhibitory effects on CYP3A4 and CYP2D6 [15]. Siberian ginseng may affect P-gp, possibly affecting levels of drugs transported by P-gp. It is advisable that caution should be used with this combination [16].  Siberian ginseng may increase the risk of bleeding or cause spontaneous haemorrhage. Concomitant use with medicines that affect haemostasis e.g. anticoagulants or antiplatelets may increase this risk [16]. |

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| **Saw palmetto:**  One *in vitro* study indicated that saw palmetto showed potent inhibition of the activities of CYP3A4, CYP2D6 and CYP2C9 suggesting the potential for drug interactions. However a small study in 12 healthy humans did not find any significant effects on CYP1A2, CYP2D6, CYP2E1 and CYP3A4 activity [1].  There is a case report of intraoperative haemorrhage, anticoagulant effects and prolonged bleeding time in one patient, and haematuria and coagulopathy in another patient who were both taking saw palmetto for benign prostatic hyperplasia [14]. Saw palmetto might increase the risk of bleeding when used concomitantly with anticoagulant or antiplatelet drugs [14].  There is also one case report of isolated hemopericardium associated with rivaroxaban in a patient who was also taking saw palmetto. The concurrent use of this herb may have contributed to the bleed by increasing rivaroxaban activity [17]. |
| **St. John’s wort:**  St John’s wort is known to affect several CYP450 isoenzymes. It is thought to exert a biphasic effect on these isoenzymes, with inhibition occurring with the initial exposure and induction following long term use. The main clinically relevant effect is the induction of CYP3A4. This is related to its hyperforin content. There are some clinical reports suggesting that St John’s wort induces CYP2C19, and it also might induce CYP2C9, CYP2E1 and CYP1A2 [15].  St. John's wort is known to affect P-gp activity, especially intestinal P-gp. It is generally thought that inhibition takes place initially and briefly but is followed by a more potent and longer-acting induction [15]. This results in decreased absorption and lowered plasma concentrations of certain medicines [14].  Plasma concentration of dabigatran, rivaroxaban, apixaban and edoxaban may be reduced by St. John's wort. The manufacturers of the NOACs give specific advice on use with St. John’s wort:  • Concomitant use with dabigatran should be avoided [9].  • Concomitant use with rivaroxaban should be avoided unless the patient is closely observed for signs and symptoms of thrombosis [10].  • In patients taking St. John’s wort, apixaban should be used with caution for the prevention of stroke and systemic embolism in patients with NVAF and for the prevention of recurrent DVT and PE. Apixaban is not recommended for the treatment of DVT and PE in patients taking St John’s wort, since efficacy may be compromised [11].  • Edoxaban should be used with caution when co-administered with P-gp inducers such as St. John’s wort as this may lead to reduced edoxaban plasma concentrations [12]. |

## Summary

* There is a lack of scientific evidence of the safety and efficacy of herbal medicines together with an under-reporting and underestimation of adverse effects. Interactions between herbal medicines and conventional medicines are poorly studied and may be unpredictable.
* The clinical importance of any interaction depends on a variety of factors, such as other co-administered medicines, the health status of the patient, the composition of the herbal medicine and the dosage regimens used.
* A lack of a documented interaction with a medicine does not mean that an interaction does not exist; it may not yet have been reported.
* Currently, four non-VKA oral anticoagulant (NOAC) drugs are available on the UK market as alternatives to warfarin: dabigatran, rivaroxaban, apixaban and edoxaban.
* The metabolic pathways of the NOACs raise concerns for potential interactions with other substances that are inducers or inhibitors of CYP450 or P-gp.
* Dabigatran is not metabolised by CYP450, so has low potential for clinically relevant interactions with medicines metabolised by CYP450. However, dabigatran etexilate is a substrate for P-gp.
* Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms and is a substrate of P-gp.
* Apixaban is predominantly metabolised by CYP3A4/5, and to a lesser extent other CYP isoenzymes. It is also a substrate of P-gp.
* Edoxaban is not extensively metabolised by CYP3A, but it is a substrate for P-gp.
* The manufacturers of all of the NOACS make specific recommendations in their SPCs regarding concurrent use with St John’s Wort due to its effect on CYP450 isoenzymes and P-gp.
* Other commonly used herbs which may affect CYP3A4, other CYP enzymes and/or P-gp include black cohosh, dong quai, echinacea, evening primrose oil, garlic, ginkgo, ginseng and saw palmetto. Although the risk of interactions appears theoretical, patients should be monitored for any adverse effects e.g. bruising, bleeding, or loss of efficacy e.g. signs and symptoms of thrombosis, if concurrent treatment with the herbal medicine cannot be avoided.
* Concomitant administration of NOACs with herbs which have anticoagulant or antiplatelet activity e.g. dong quai, garlic, ginkgo, ginseng, saw palmetto and evening primrose oil, may increase the risk of bleeding and should be avoided or used with caution.

Limitations

* Co-administration of dabigatran, rivaroxaban, apixaban or edoxaban with herbal medicines has not been investigated in clinical studies; consequently a lack of a documented interaction with a drug may not mean that an interaction does not exist, only that it has not yet been reported.
* This Q&A is not exhaustive, other herbal medicines which are not discussed in this Q&A may also interact with NOACs.

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### Search strategy

* Embase (via HDAS): [exp ANTITHROMBINS or exp "BLOOD CLOTTING FACTOR 10A INHIBITOR" or exp "DABIGATRAN " or exp RIVAROXABAN or exp APIXABAN or exp EDOXABAN] and [exp "HERBAL MEDICINE" or exp "DIETARY SUPPLEMENT"]
* Medline: [exp ANTITHROMBINS or exp "FACTOR XA INHIBITORS" or exp DABIGATRAN or exp RIVAROXABAN or (edoxaban).ti,ab or (apixaban).ti,ab] and [exp "HERBAL MEDICINE" or exp "DIETARY SUPPLEMENTS"]
* In-house database/ resources
* British National Formulary online, Martindale The Complete Drug Reference, Herbal Medicines, Stockley’s Herbal Medicines Interactions: accessed via [www.medicinescomplete.com](http://www.medicinescomplete.com/),
* Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA.