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Review

INTERACTION BETWEEN WARFARIN AND SELECTED SUPERFOODS: A COMPREHENSIVE REVIEW OF POTENTIAL MECHANISMS AND THEIR CLINICAL SIGNIFICANCE

Dariusz Łaszczych*[1]†, Aleksandra Czernicka[1]†, Kornelia Kędziora-Kornatowska[1]

[1] *Department and Clinic of Geriatrics, Faculty of Health Sciences, Nicolaus Copernicus University in Toruń, Ludwik Rydygier Collegium Medicum in Bydgoszcz, 85-094 Bydgoszcz, Poland*

† These authors contributed equally

* Correspondence, e-mail: laszczychdariusz@gmail.com

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ABSTRACT

Warfarin is one of the oldest and still widely used anticoagulant agents. Interactions between warfarin and herbs have been intensively studied in recent years. However, due to the growing worldwide interest and consumption of herbal products this area requires further investigations. Patients on warfarin should receive special attention from their physicians, especially concerning the concomitant use of herbal products. In this study, we provide a comprehensive review of the mechanisms and clinical significance of interactions between warfarin and selected plants, also frequently referred to as *superfoods*: *Linum usitatissimum, Moringa oleifera, Lindera aggregata,* and *Nigella sativa*. We carried out a non-systematic review of the literature using PubMed using the key terms: warfarin, interaction, *Linum usitatissimum, Moringa oleifera, Lindera aggregata, Nigella sativa*, CYP2C9, CYP3A4, serum albumin, blood coagulation, antiplatelet. We analyzed articles published up to 2024. The wealth of phytoconstituents contained in reviewed plants favor the occurrence of potential interactions with warfarin. Possible mechanisms involved in these interactions include plasma and platelet hemostasis processes and warfarin pharmacokinetics, i.e. distribution and hepatic metabolism. Critical evaluation of the risk of warfarin-herb interaction is challenging and still inconclusive because most of the sources of evidence are *in vitro* and animal studies. Therefore we expect human clinical studies evaluating the risk of combined use of warfarin and discussed plants in the near future. To summarize, we hope that the results of our study will help healthcare professionals in their daily practice and improve the safety and effectiveness of warfarin pharmacotherapy.

KEYWORDS: Warfarin, Herb-drug interaction, *Linum usitatissimum*, *Moringa oleifera*, *Nigella sativa*

1. Introduction

Warfarin is one of the first anticoagulant drugs applied in clinical practice [1]. Warfarin is indicated e.g. in the treatment of venous thromboembolism and the prevention of ischemic strokes among patients with atrial fibrillation [2]. Currently, we can observe the tendency to replace warfarin with novel oral anticoagulants (NOACs) in the indications mentioned above [3]. Regardless of the benefits of using NOACs, warfarin remains the first line of therapy in valvular atrial fibrillation, antiphospholipid syndrome, and in the case of artificial heart valves [4]. The cost of novel anticoagulants both for patients and the healthcare systems restricts the opportunity to switch from warfarin to NOACs for the majority of patients [5]. The low cost of therapy is one of the main reasons why warfarin is still widely used in clinical practice. Warfarin therapy is associated with several problems. Patients should strictly adhere to the correct intake of warfarin. The omission of doses may decrease the warfarin anticoagulation effect. On the contrary, an overdose of warfarin may lead to adverse events such as gastrointestinal (GI) bleeding, hematuria, or even intracranial bleeding [6]. Another issue is potential drug interactions. Coadministered drugs may affect both the absorption and metabolism of warfarin affecting the efficacy or safety of therapy [7]. Other important factors that may compromise therapy with warfarin are food, dietary supplements, and herbal medicines consumed by the patient. Therefore patients should consult with a physician before making major changes in their diet or

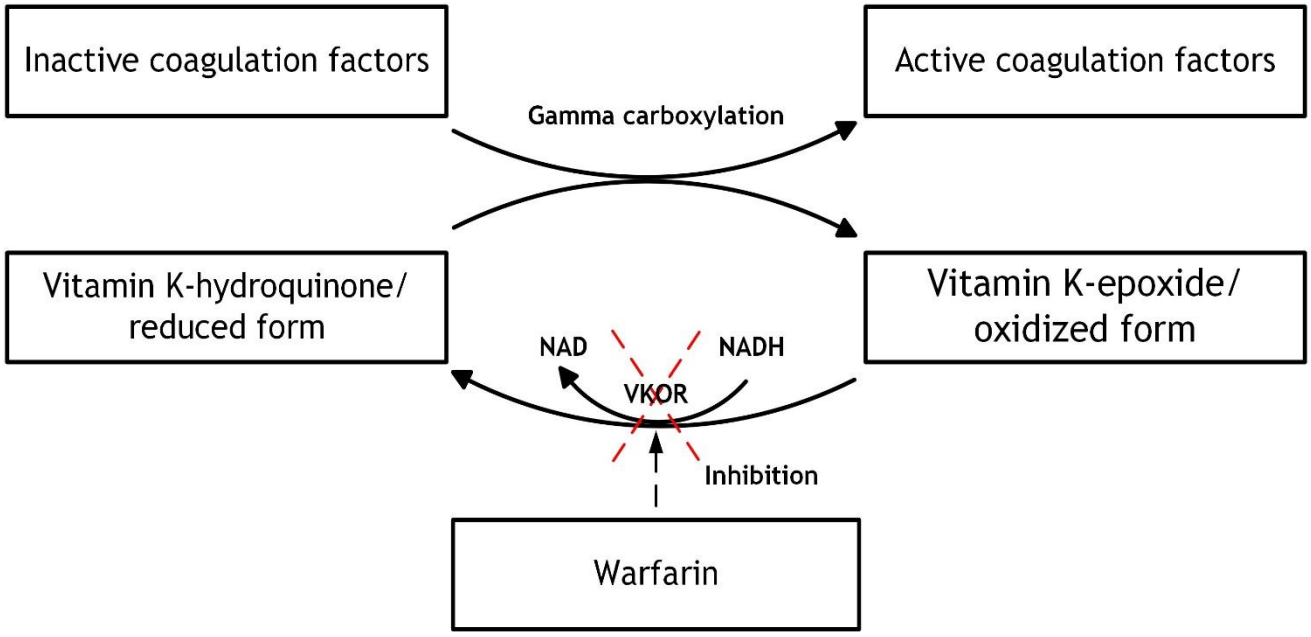

Fig 1. The mechanism of action of warfarin. VKOR – vitamin K epoxide reductase, NAD - Nicotinamide adenine dinucleotide, NADH - reduced form of NAD.

implementing herbal medicines. Awareness of both patient and doctor about possible herb-warfarin interaction may contribute to improving the efficacy and safety of anticoagulant therapy. Due to the rapidly growing worldwide interest in herbal products and medicines, it is crucial to identify potential herb-drug interactions. It is of particular importance in the case of drugs with a narrow therapeutic index such as warfarin. Our work aims to review novel scientific reports regarding possible interactions between warfarin and selected plants and the mechanisms underlying them. Since many potential herb-warfarin interactions have been described in the literature so far, in our work we focus on less studied plants: *Linum usitatissimum*, *Moringa oleifera, Lindera aggregata,* and *Nigella sativa*. By providing new insight into the interaction between warfarin and plant products we intend to raise awareness among healthcare professionals and their patients.

2. Warfarin - overview

Warfarin is a coumarin derivative organic compound belonging to the vitamin K antagonist (VKA). Its anticoagulant activity is based on inhibiting vitamin K epoxide reductase (VKOR). VKOR catalyzes the conversion of vitamin K-epoxide to vitamin K hydroquinone, which is a biologically active form of vitamin K. Active vitamin K is involved in post-translational gamma-carboxylation of several human proteins, especially coagulation factors II, VII, IX, and X. Warfarin by inhibition of VKOR decreases the amount of vitamin K hydroquinone (Figure 1). The lack of a reduced form of vitamin K impairs the gamma-carboxylation process required to confer biological activity of coagulation factors II, VII, IX, and X. Decrease of the intrinsic activity of these coagulation factors results in a disorder of the blood coagulation process and is responsible for warfarin anticoagulant activity [8].

2.1 Pharmacokinetics

After oral administration, warfarin is almost completely absorbed in the gastrointestinal tract. About 99% of warfarin is bound to serum proteins, especially serum albumin. Warfarin is metabolized in the liver by cytochrome P450 (CYP) enzymes. The main CYP isoenzyme involved in the warfarin metabolism is CYP2C9. CYP2C9 through 7-hydroxylation of S-warfarin leads to the generation of 7-hydroxywarfarin. CYP1A2, CYP2C19, and CYP3A4 also metabolize warfarin [9]. Warfarin is almost completely metabolized in the human body to secondary metabolites. Warfarin is eliminated predominantly with urine (80%) and feces (20%) [10].

2.2 Mechanisms of interactions

Due to both complex pharmacokinetic and dynamic profiles of warfarin, many factors including genetics, dietary habits, drugs, and patient comorbidities may affect both warfarin intrinsic activity and therapy safety. Most pharmacokinetic interactions occur through the inhibition or induction of warfarin liver metabolism. For example, the induction of CYP2C9 increases the clearance of warfarin and reduces its anticoagulant activity. On the other side, CYP2C9 inhibition increases the serum concentration of warfarin. Another pharmacokinetic interaction may occur through alternation of warfarin distribution in the body. Some agents/xenobiotics, because of their higher affinity, may displace the warfarin from the bound with plasma proteins (mainly albumins). Moreover, changes in the serum concentration of albumins, which are the main drug carriers in the human body, affect the amount of unbound, i.e. biologically active, warfarin fraction. Among pharmacodynamic interactions, we can distinguish e.g. dietary intake of products rich in vitamin K. Exogenous vitamin K acts as a competitive antagonist of warfarin. On the other side, coadministration of drugs that impair platelet aggregation such as aspirin, ticagrelor, or clopidogrel may significantly alter blood coagulation and increase the risk of adverse events such as GI bleeding, intramuscular hematomas or hematuria [11,12]. The multitude of factors affecting the safety and effectiveness of pharmacotherapy implies the need for close monitoring of blood coagulation parameters during warfarin therapy.

3. Concomitant use of selected plants and warfarin - mechanisms of potential interaction and its significance

3.1 *Linum usitatissimum*

Linum usitatissimum, or flax, is one of the oldest fibrous plants cultivated for its fiber and flaxseed [13]. Flaxseed is a storehouse for many phytonutrients such as linoleic acid, cyclic peptides, alkaloids, lignans such as secoisolariciresinol diglucoside (SDG), and plant omega-3 alpha-linolenic acid (ALA) [14,15]. So far, the hypotensive activity of flaxseed has been broadly studied [16]. In addition, flaxseed has a positive effect on the course of lifestyle diseases such as diabetes [17]. Despite a positive impact of flax on our health, recent reports indicate that certain patients should avoid flax-derived products. It seems that patients who should be especially careful are those requiring anticoagulation or antiplatelet therapy. Recently, it has been demonstrated that flaxseed cysteine protease (FSCP), isolated from *L. usitatissimum* seeds, exhibits anticoagulant activity. FSCP incubated with human plasma significantly prolonged clotting time and activated partial thromboplastin time (aPTT) and prothrombin time (PT). FSCP anticoagulant activity was also proven *in vivo* in murine model [18,19]. The latest report from Nandish et al. indicates that apart from FSCP, flaxseed contains other bioactive molecules that may alter both primary and secondary hemostasis [20]. Consuming flaxseed may potentially impact blood clotting due to its abundant ALA content. To date, few studies investigated the impact of ALA on blood coagulation or platelet aggregation. Dietary ALA may inhibit arterial thrombosis formation *in vivo* through the downregulation of tissue factor (TF) expression. ALA may also attenuate the aggregation of thrombocytes [20]. Yang et al. reported that ALA impairs platelet activity *in vivo* [22]. Recently, Stivala et al. showed that the anti-platelet activity of ALA may be associated with the decreased endothelial expression of von Willebrand factor (vWF). vWF is a pivotal factor in platelet hemostasis including adhesion and aggregate formation. Impairment of platelet function through downregulation of wVF may result in coagulation disorder. The potential synergetic effect of ALA and warfarin on the hemostasis process may increase the risk of adverse events [23]. Apart from direct influence at hemostasis, it has been demonstrated that phytoconstituents present in flaxseed may affect warfarin metabolism. Recent research indicates that SDG may induce the expression of CYP2C9 and CYP3A4 *in vitro* [24]. Furthermore, Aqeel et al. showed that SDG can increase serum albumin concentration [25]. The increased level of serum albumin may result in a higher protein-bound warfarin fraction. Since protein-bound drugs do not exhibit intrinsic activity, an increased percentage of albumin-bound warfarin fraction may result in attenuated warfarin anticoagulant activity [26]. In summary, results show that consumption of *Linum usitatissimum* products can affect the efficacy and safety of warfarin therapy in two opposite ways. Some of the flax phytoconstituents indicate antiplatelet and anticoagulant activity *in vivo*. The synergistic effects of flax and warfarin may increase the risk of adverse events. On the other hand, some studies suggest that flaxseed consumption may result in decreased effectiveness of anticoagulant therapy. So far, the significance of the potential interaction between flaxseed and warfarin has not been defined. Wide consumption of flax-derived products may be unfavorable for certain groups of patients. Due to ambiguous results of *in vitro* and animal studies, further research is needed to evaluate the clinical significance of flax-warfarin interaction.

3.2 *Moringa oleifera*

Moringa oleifera, also known as a drumstick or horseradish tree, is a cruciferous plant cultivated mainly in the Middle East and Asian countries [27]. *M. oleifera* leaves are a rich storehouse of omega-3 and omega-6 polyunsaturated fatty acids [28]. The results of a recent meta-analysis indicate that consumption of *M.oleifera* leaf powder may be promising adjuvant therapy in prediabetic and diabetic patients [29]. In addition, numerous investigations have revealed anti-inflammatory, antioxidant, anticancer, antimicrobial, and hepatoprotective properties of *M. oleifera* [30]. Thanks to the presence of various phytoconstituents, *M. oleifera* has a positive impact on our health and can be beneficial to patients suffering from many diseases. On the other side, *Moringa* consumption may potentially interfere with drugs taken by patients. Monera et al. showed that *M. oleifera* extract significantly inhibits the activity of CYP3A4 *in vivo* [31]. Fantoukh et al. reported that newly isolated *Moringa*-derived compounds exhibit significant inhibitory activity on CYP3A4 *in vitro* [32]. In addition, *Moringa* extract inhibits the activity of CYP1A2 and CYP2C9 *in vitro*. Notably, the theoretical evaluation of inhibitory potential suggests that the extract of *M. oleifera* may also affect the activity of CYP1A2 and CYP2C9 *in vivo*. Since warfarin is metabolized mainly through CYP2C9, CYP1A2, and CYP3A4 isoenzymes, therefore concomitant use with *Moringa* products may potentially increase the serum concentration of warfarin. However, to evaluate the clinical significance of the potential interaction between *Moringa* and warfarin further investigations are needed [33,34]. Results of a recent study suggest that *Moringa* may also affect warfarin distribution. Asare et al. showed that *M.oleifera* may alter serum albumin concentration. Rats treated with high doses of *Moringa* leaf extract had significantly decreased concentrations of albumin compared to the control [35]. A decreased concentration of serum albumin may result in a higher protein-unbound warfarin fraction and therefore enhanced anticoagulant activity of warfarin. By the impact on both primary and secondary hemostasis, phytoconstituents can alter the blood coagulation process. Cotabarren et al. in the recently published study isolated and characterized new phytocystatin from *M.oleifera* seeds. The newly discovered phytocystatin, named *M. oleifera* papain inhibitor (MoPI), was responsible for the significant prolongation of aPTT in the blood sample collected from healthy donors. However, the mechanisms underlying the anticoagulant activity of MoPI remain unknown and require further investigation [36,37]. Due to the wealth of phytonutrients, the consumption of *M. oleifera* can be beneficial to our health. However, it seems that in several situations *Moringa* intake should be avoided. The consumption of *Moringa* through changes in the drug metabolism and distribution is likely to result in the supra-therapeutic concentration of warfarin. Moreover, the newly described MoPI may have a synergistic effect with warfarin. However, due to the limitations of *in vitro* studies, the clinical significance of the potential interaction between warfarin and *M. oleifera* should be evaluated in further investigations.

3.3 *Lindera agregata*

Lindera aggregata is a plant used in traditional Chinese medicine for centuries. The most valuable parts of the plant are the roots and leaves. The dried root of *Lindera* is indicated in disorders of the gastrointestinal tract and urinary system. The leaves may be a relief for skin diseases and rheumatoid arthritis. Previous studies indicate that the phytoconstituents responsible for various biological properties of *Lindera* are sesquiterpenoids, found mostly in the roots of the plant. To date, more than 100 sesquiterpenoids have been identified. Sesquiterpenoids exhibit many beneficial activities, e.g. hepatoprotective, antibacterial, antiviral, anti-oxidative, and anti-inflammatory [38,39]. *L. aggregata*-derived sesquiterpenoids are being extensively investigated for other biological properties such as anticoagulant activity. A recent study revealed that a newly discovered sesquiterpene dimer named linderin B may prolong aPTT time *in vitro* [40]. By impairing the coagulation cascade, *L. aggregata* can decrease the risk of thromboembolic events. Conversely, the potential synergetic effect of *L. aggregata* and anticoagulants such as warfarin may increase the risk of serious adverse events such as GI or intracranial bleeding. Discussing *L. aggregata* and its potential interaction with warfarin, attention should be paid to phytoconstituents with furanoid structure. It is widely known that furan-containing molecules can inhibit the activity of CYP450 isoenzymes through specific, irreversible mechanism-based inactivation (MBI). Furanoids are metabolized by CYP450 to reactive intermediates, which can further covalently bind to key amino acids in the active site of cytochromes. Biochemical modification of the active site results in irreversible enzyme inactivation [41]. Wang et al. showed that linderane (LDR), a sesquiterpenoid found in the roots of *L. aggregata*, is preferentially metabolized through CYP2C9 and CYP3A4. Moreover, CYP2C9 activity was decreased after prior incubation with LDR. It is noted that CYP2C9 inhibition was observed only when NADPH was present in the incubation mixtures. It implies that the presence of reactive LDR intermediates is essential for enzyme inhibition. In addition, it has been demonstrated that the LDR-mediated CYP2C9 inactivation was irreversible [42]. Recently, it has been demonstrated that LDR may affect warfarin metabolism *in vivo* through CYP2C9 inactivation. Notable, mice treated with LDR were characterized with significantly decreased expression of CYP2C9 protein compared to the control group [43]. Taken together, the inhibitory effect of LDR on CYP2C9 activity observed *in vivo* poses a risk of potential interaction with warfarin. Since LDR is considered one of the main active compounds in *L. aggregata*, patients should be closely monitored in case of the concomitant use of warfarin and *Lindera*-derived herbal products or medicines.

3.4 *Nigella sativa*

Nigella sativa (NS), also known as black cumin or black seeds, is an annual flowering plant valued for its culinary use and medicinal properties. NS in the form of oil, powder, or extract is used in ethnomedicine to treat e.g. allergies, rheumatism, hypertension, and gastrointestinal disorders [44]. The positive impact of *Nigella* on human health postulated by traditional medicine has been confirmed by scientific investigations. Furthermore, it has been shown that the phytoconstituent responsible for various pharmacological activities of *Nigella* is thymoquinone (TQ), a major compound found in *Nigella* essential oils. TQ exhibits antioxidant, anti-cancer, anti-inflammatory, antimicrobial, and cardioprotective properties [45]. Despite many pro-health properties, black seed consumption may affect the safety and effectiveness of warfarin therapy. Recently it has been demonstrated that TQ is responsible for aPTT prolongation and inhibition of factor X activity *in vitro* [46]. TQ may also affect platelet hemostasis. TQ through activation of caspase-3 promotes platelet destruction [47]. TQ alters platelet function in several additional mechanisms. TQ increases the concentration of phosphatidylserine on the platelet surface. Upregulation of phosphatidylserine leads to platelet apoptosis [48]. Wang et al. showed that TQ may interact with warfarin by inhibiting the activity of CYP2C9 and CYP3A4. Regarding the safe daily consumption of black cumin, it seems that consumption of up to 18 mg/day of pure TQ and up to 1 g/day of *N. sativa* extract is not likely to result in interaction with warfarin. Exceeding the recommended dose may result in significant side effects [49]. Furthermore, *N. sativa* extract, apart from modulating the activity of cytochrome isoenzymes, may also regulate the expression of cytochrome genes [50,51]. Al-Jenoobi et al. in their clinical trial showed that phytoconstituents present in *N. sativa* have an inhibitory effect on CYP3A4 *in vivo*. Concomitant use of dextromethorphan and black cumin resulted in a decreased concentration of dextromethorphan metabolites in urine samples [52]. Results of that clinical trial suggest that NS consumption may affect warfarin metabolism since dextromethorphan and warfarin have a common metabolic pathway through CYP3A4. However, to evaluate the clinical significance of that potential interaction between NS and warfarin further investigations are necessary. In summary, the impact of thymoquinone on coagulation factors, platelet homeostasis, and cytochrome isoenzyme activity are only a few of the potential mechanisms underlying warfarin-*Nigella* interaction. However, the significance of this interaction needs to be fully elucidated.

4. Conclusions

To date, numerous clinically important interactions between warfarin and herbal products have been described in the literature. However, because of growing interest in herbal products/medicines and easy access to various exotic plant products, further research on warfarin-herbs interaction is needed. In this article, we discussed the mechanisms of potential interaction between warfarin and *Linum usitatissimum, Moringa oleifera, Lindera aggregata, and Nigella sativa*. Our findings are summarized in Table 1. To our knowledge, it is the first work to study mechanisms of interaction between warfarin and the above-mentioned herbs in such a comprehensive way. Results indicate that herbs discussed in this review should be used with caution in patients on warfarin therapy. Concomitant use of these medicinal herbs can either decrease the effectiveness or safety of anticoagulant therapy. Herbs may affect the blood coagulation process which is manifested in prolongation of aPTT or PT time. Furthermore, herbs impair platelet hemostasis including adhesion and aggregation of thrombocytes. Other mechanisms underlying potential interactions are related to the pharmacokinetics of warfarin. Phytoconstituents can either inhibit or induce the activity of several cytochrome isoenzymes engaged in warfarin metabolism. Moreover, herbal bioactive molecules

Table 1. Potential herbal interaction with warfarin

Scientific name	Common name	Plant derivative/ phytoconstituent	Mechanism	Possible interaction with warfarin	Source of evidence	Reference
Linum usitatissimum	Flax	Flaxseed extract - cysteine protease	Prolonged aPTT and PT	Increased risk of bleeding	*in vitro*, *in vivo* (animals)	[17,18]
		Alpha-linolenic acid	Downregulation of tissue factor, decreased platelet aggregation and activity	Increased risk of bleeding	*in vitro*, *in vivo*	[20,21]
		Alpha-linolenic acid	Decreased platelet adhesion by downregulation of vWF	Increased risk of bleeding	*in vitro*	[22]
		Flaxseed- SDG lignan	CYP2C9 and CYP3A4 induction	Decreased anticoagulant activity of warfarin	*in vitro*	[23]
		Flaxseed - SDG lignan	Increased serum albumin concentration - warfarin distribution	Decreased anticoagulant activity of warfarin	*in vivo*	[24]
Moringa oleifera	drumstick, horseradish tree	Leaf extract	CYP3A4 inhibition	Increased risk of bleeding	*in vitro*, *in vivo*	[30,31]
		Leaf extract	CYP1A2 and CYP2C9 inhibition	Increased risk of bleeding	*in vitro*	[32,33]
		Leaf extract	Decreased serum albumin concentration - warfarin distribution	Increased risk of bleeding	*in vivo* (animals)	[34]
		Seeds extract - phytocystatin MoPI	Prolonged aPTT	Increased risk of bleeding	*in vitro*	[35]
Lindera aggregata	Japanese evergreen spicebush	Root - sesquiterpene linderin B	Prolonged aPTT	Increased risk of bleeding	*in vitro*	[39]
		Root - sesquiterpene LDR	CYP2C9 inhibition (mechanism-based inactivation), downregulation of CYP2C9 expression	Increased risk of bleeding	*in vitro*, *in vivo* (animals)	[41,42]
Nigella sativa	black seeds, black cumin	Thymoquinone	Prolonged aPTT, inhibition of factor X activity	Increased risk of bleeding	*in vitro*	[45]
		Thymoquinone	Antiplatelet effect	Increased risk of bleeding	*in vitro*	[46,47]
		Thymoquinone	CYP2C9 and CYP3A4 inhibition	Increased risk of bleeding	*in vitro -in vivo* extrapolation	[48]
		Seeds	CYP3A4 inhibition	Increased risk of bleeding	*in vitro, in vivo (*human)	[51]

modulate warfarin distribution through changes in the concentration of the unbound fraction of warfarin. Notably, the clinical significance of the potential interaction between described herbs and warfarin is inconclusive. This is due to the relatively limited number of research in the literature and the lack of human studies which are the most reliable scientific source. Since a better understanding of the risk of interaction in concomitant use of warfarin and herbal medicines/products may help avoid adverse events and increase the effectiveness of anticoagulant therapy we expect more research in this area in the future. To sum up, the patients on warfarin therapy are at risk of potential interactions with herbal medicines, products, and supplements. To improve patient care physicians should promote the rational use of herbal medicines/products. Both healthcare professionals and patients should be aware of medicinal plants that may cause life-threatening adverse events including GI and intracranial bleeding. Close collaboration between doctor and patient can contribute to improving the quality of care and optimizing the safety and effectiveness of anticoagulant pharmacotherapy with warfarin.

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References

1. Franchini, M.; Liumbruno, G. M.; Bonfanti, C.; Lippi, G. The Evolution of Anticoagulant Therapy. *Blood Transfus.* **2016**, *14* (2), 175–184. https://doi.org/10.2450/2015.0096-15.
2. Pengo, V.; Denas, G. Optimizing Quality Care for the Oral Vitamin K Antagonists (VKAs). *Hematol. Am. Soc. Hematol. Educ. Program* **2018**, *2018* (1), 332–338.
3. López-López, J. A.; Sterne, J. A. C.; Thom, H. H. Z.;

Higgins, J. P. T.; Hingorani, A. D.; Okoli, G. N.; Davies, P. A.; Bodalia, P. N.; Bryden, P. A.; Welton, N. J.; Hollingworth, W.; Caldwell, D. M.; Savović, J.; Dias, S.; Salisbury, C.; Eaton, D.; Stephens-Boal, A.; Sofat, R. Oral Anticoagulants for Prevention of Stroke in Atrial Fibrillation: Systematic Review, Network Meta-Analysis, and Cost Effectiveness Analysis. *The BMJ* **2017**, *359*, j5058. https://doi.org/10.1136/bmj.j5058.

4. Wadsworth, D.; Sullivan, E.; Jacky, T.; Sprague, T.; Feinman, H.; Kim, J. A Review of Indications and Comorbidities in Which Warfarin May Be the Preferred Oral Anticoagulant. *J. Clin. Pharm. Ther.* **2021**, *46* (3), 560–570. https://doi.org/10.1111/jcpt.13343.

5. Pyykönen, M.; Linna, M.; Tykkyläinen, M.; Delmelle, E.; Laatikainen, T. Patient-Specific and Healthcare Real-World Costs of Atrial Fibrillation in Individuals Treated with Direct Oral Anticoagulant Agents or Warfarin. *BMC Health Serv. Res.* **2021**, *21* (1), 1299. https://doi.org/10.1186/s12913-021-07125-5

6. Ababneh, M.; Nasser, S. A.; Rababa'h, A.; Ababneh, F. Warfarin Adherence and Anticoagulation Control in Atrial Fibrillation Patients: A Systematic Review. *Eur. Rev. Med. Pharmacol. Sci.* **2021**, *25* (24), 7926–7933. https://doi.org/10.26355/eurrev_202112_27642.

7. Juurlink, D. N. Drug Interactions with Warfarin: What Clinicians Need to Know. *CMAJ Can. Med. Assoc. J.* **2007**, *177* (4), 369–371. https://doi.org/10.1503/cmaj.070946.

8. Donaldson, C. J.; Harrington, D. J. Therapeutic Warfarin Use and the Extrahepatic Functions of Vitamin K-Dependent Proteins. *Br. J. Biomed. Sci.* **2017**, *74* (4), 163–169. https://doi.org/10.1080/09674845.2017.1336854.

9. Porter, W. R. Warfarin: History, Tautomerism and Activity. *J. Comput. Aided Mol. Des.* **2010**, *24* (6–7), 553–573. https://doi.org/10.1007/s10822-010-9335-7.

10. Ufer, M. Comparative Pharmacokinetics of Vitamin K Antagonists: Warfarin, Phenprocoumon and Acenocoumarol. *Clin. Pharmacokinet.* **2005**, *44* (12), 1227–1246. https://doi.org/10.2165/00003088-200544120-00003.

11. Tadros, R.; Shakib, S. Warfarin--Indications, Risks and Drug Interactions. *Aust. Fam. Physician* **2010**, *39* (7), 476–479.

12. Jacobs, L. G. Warfarin Pharmacology, Clinical Management, and Evaluation of Hemorrhagic Risk for the Elderly. *Cardiol. Clin.* **2008**, *26* (2), 157–167, v. https://doi.org/10.1016/j.ccl.2007.12.010.

13. Saleem, M. H.; Ali, S.; Hussain, S.; Kamran, M.; Chattha, M. S.; Ahmad, S.; Aqeel, M.; Rizwan, M.; Aljarba, N. H.; Alkahtani, S.; Abdel-Daim, M. M. Flax (*Linum Usitatissimum* L.): A Potential Candidate for Phytoremediation? Biological and Economical Points of View. *Plants* **2020**, *9* (4), 496. https://doi.org/10.3390/plants9040496.

14. Gebauer, S. K.; Psota, T. L.; Harris, W. S.; Kris-Etherton, P. M. N−3 Fatty Acid Dietary Recommendations and Food Sources to Achieve Essentiality and Cardiovascular Benefits. *Am. J. Clin. Nutr.* **2006**, *83* (6), 1526S-1535S. https://doi.org/10.1093/ajcn/83.6.1526S.

15. Imran, M.; Ahmad, N.; Anjum, F. M.; Khan, M. K.; Mushtaq, Z.; Nadeem, M.; Hussain, S. Potential Protective Properties of Flax Lignan Secoisolariciresinol Diglucoside. *Nutr. J.* **2015**, *14*, 71. https://doi.org/10.1186/s12937-015-0059-3.

16. Parikh, M.; Netticadan, T.; Pierce, G. N. Flaxseed: Its Bioactive Components and Their Cardiovascular Benefits. *Am. J. Physiol.-Heart Circ. Physiol.* **2018**, *314* (2), H146–H159. https://doi.org/10.1152/ajpheart.00400.2017.

17. Parikh, M.; Maddaford, T. G.; Austria, J. A.; Aliani, M.; Netticadan, T.; Pierce, G. N. Dietary Flaxseed as a Strategy for Improving Human Health. *Nutrients* **2019**, *11* (5), 1171. https://doi.org/10.3390/nu1105117

18. Nandish, S. K. M.; Kengaiah, J.; Ramachandraiah, C.; Shivaiah, A.; Chandramma; Girish, K. S.; Kemparaju, K.; Sannaningaiah, D. Anticoagulant, Antiplatelet and Fibrin Clot Hydrolyzing Activities of Flax Seed Buffer extract. *Pharmacogn. Mag.* **2018,** 14 (55), 175. https://doi.org/10.4103/pm.pm_320_17

19. Nandish, S. K. M.; Kengaiah, J.; Ramachandraiah, Ch.; Chandramma; Shivaiah, A.; Santhosh, S. M.; Thirunavukkarasu; Sannaningaiah, D. Flaxseed Cysteine Protease Exhibits Strong Anticoagulant, Antiplatelet, and Clot-Dissolving Properties. *Biochem. Mosc.* **2020**, *85* (9), 1113–1126. https://doi.org/10.1134/S0006297920090102.

20. Nandish, S. K. M.; Kengaiah, J.; Ramachandraiah, C.; Chandramma; Shivaiah, A.; Thirunavukkarasu; Shankar, R. L.; Sannaningaiah, D. Purification and Characterization of Non-Enzymatic Glycoprotein (NEGp) from Flax Seed Buffer Extract That Exhibits Anticoagulant and Antiplatelet Activity. *Int. J. Biol. Macromol.* **2020**, *163*, 317–326. https://doi.org/10.1016/j.ijbiomac.2020.06.270.

21. Holy, E. W.; Forestier, M.; Richter, E. K.; Akhmedov, A.; Leiber, F.; Camici, G. G.; Mocharla, P.; Lüscher, T. F.; Beer, J. H.; Tanner, F. C. Dietary α-Linolenic Acid Inhibits Arterial Thrombus Formation, Tissue Factor Expression, and Platelet Activation. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31* (8), 1772–1780. https://doi.org/10.1161/ATVBAHA.111.226118.

22. Yang, Q.; Cao, W.; Zhou, X.; Cao, W.; Xie, Y.; Wang, S. Anti-Thrombotic Effects of α-Linolenic Acid Isolated from Zanthoxylum Bungeanum Maxim Seeds. *BMC Complement. Altern. Med.* **2014**, *14*, 348. https://doi.org/10.1186/1472-6882-14-348.

23. Stivala, S.; Gobbato, S.; Bonetti, N.; Camici, G. G.; Lüscher, T. F.; Beer, J. H. Dietary Alpha-Linolenic Acid Reduces Platelet Activation and Collagen-Mediated Cell Adhesion in Sickle Cell Disease Mice. *J. Thromb. Haemost. JTH* **2022**, *20* (2), 375–386. https://doi.org/10.1111/jth.15581.

24. Defries, D.; Shariati, S.; Blewett, H.; Aliani, M. Expression of Cytochrome P450 Enzymes Is Induced by Flaxseed Enterolignans. *Curr. Dev. Nutr.* **2021**, *5* (Suppl 2), 312. https://doi.org/10.1093/cdn/nzab037_022.

25. Aqeel, T.; Chikkalakshmipura Gurumallu, S.; Hashimi, S. M.; AlQurashi, N.; Javaraiah, R. Evaluation of Protective Efficacy of Flaxseed Lignan-Secoisolariciresinol Diglucoside against Mercuric Chloride-Induced Nephrotoxicity in Rats. *Mol. Biol. Rep.* **2019**, *46* (6), 6171–6179. https://doi.org/

10.1007/s11033-019-05052-7.

26. Fender, A. C.; Dobrev, D. Bound to Bleed: How Altered Albumin Binding May Dictate Warfarin Treatment Outcome. *Int. J. Cardiol. Heart Vasc.* **2019**, *22*, 214–215. https://doi.org/10.1016/j.ijcha.2019.02.007

27. Rode, S. B.; Dadmal, A.; Salankar, H. V. Nature's Gold (Moringa Oleifera): Miracle Properties. *Cureus* **2022**, *14* (7), e26640. https://doi.org/10.7759/cureus.26640.

28. Saini, R. K.; Sivanesan, I.; Keum, Y.-S. Phytochemicals of Moringa Oleifera: A Review of Their Nutritional, Therapeutic and Industrial Significance. *3 Biotech* **2016**, *6* (2), 203. https://doi.org/10.1007/s13205-016-0526-3.

29. Nova, E.; Redondo-Useros, N.; Martínez-García, R. M.; Gómez-Martínez, S.; Díaz-Prieto, L. E.; Marcos, A. Potential of Moringa Oleifera to Improve Glucose Control for the Prevention of Diabetes and Related Metabolic Alterations: A Systematic Review of Animal and Human Studies. *Nutrients* **2020**, *12* (7), 2050. https://doi.org/10.3390/nu12072050.

30. Kou, X.; Li, B.; Olayanju, J. B.; Drake, J. M.; Chen, N. Nutraceutical or Pharmacological Potential of Moringa Oleifera Lam. *Nutrients* **2018**, *10* (3), 343. https://doi.org/10.3390/nu10030343.

31. Monera, T. G.; Wolfe, A. R.; Maponga, C. C.; Benet, L. Z.; Guglielmo, J. Moringa Oleifera Leaf Extracts Inhibit 6ß-Hydroxylation of Testosterone by CYP3A4. *J. Infect. Dev. Ctries.* **2008**, *2* (5), 379–383.

32. Fantoukh, O. I.; Albadry, M. A.; Parveen, A.; Hawwal, M. F.; Majrashi, T.; Ali, Z.; Khan, S. I.; Chittiboyina, A. G.; Khan, I. A. Isolation, Synthesis, and Drug Interaction Potential of Secondary Metabolites Derived from the Leaves of Miracle Tree (Moringa Oleifera) against CYP3A4 and CYP2D6 Isozymes. *Phytomedicine Int. J. Phytother. Phytopharm.* **2019**, *60*, 153010. https://doi.org/10.1016/j.phymed.2019.153010.

33. Showande, S. J.; Fakeye, T. O.; Kajula, M.; Hokkanen, J.; Tolonen, A. Potential Inhibition of Major Human Cytochrome P450 Isoenzymes by Selected Tropical Medicinal Herbs — Implication for Herb–Drug Interactions. *Food Sci. Nutr.* **2018**, *7* (1), 44–55. https://doi.org/10.1002/fsn3.789.

34. Amaeze, O.; Eng, H.; Horlbogen, L.; Varma, M. V. S.; Slitt, A. Cytochrome P450 Enzyme Inhibition and Herb-Drug Interaction Potential of Medicinal Plant Extracts Used for Management of Diabetes in Nigeria. *Eur. J. Drug Metab. Pharmacokinet.* **2021**, *46* (3), 437–450. https://doi.org/10.1007/s13318-021-00685-1

35. Asare, G. A.; Gyan, B.; Bugyei, K.; Adjei, S.; Mahama, R.; Addo, P.; Otu-Nyarko, L.; Wiredu, E. K.; Nyarko, A. Toxicity Potentials of the Nutraceutical Moringa Oleifera at Supra-Supplementation Levels. *J. Ethnopharmacol.* **2012**, *139* (1), 265–272. https://doi.org/10.1016/j.jep.2011.11.009.

36. Cotabarren, J.; Claver, S.; Payrol, J. A.; Garcia-Pardo, J.; Obregón, W. D. Purification and Characterization of a Novel Thermostable Papain Inhibitor from Moringa Oleifera with Antimicrobial and Anticoagulant Properties. *Pharmaceutics* **2021**, *13* (4), 512. https://doi.org/10.3390/pharmaceutics13040512.

37. Hellinger, R.; Gruber, C. W. Peptide-Based Protease Inhibitors from Plants. *Drug Discov. Today* **2019**, *24* (9), 1877–1889. https://doi.org/10.1016/j.drudis.2019.05.026.

38. Lv, Y.; Zou, Y.; Zhang, X.; Liu, B.; Peng, X.; Chu, C. A Review on the Chemical Constituents and Pharmacological Efficacies of Lindera Aggregata (Sims) Kosterm. *Front. Nutr.* **2023**, *9*, 1071276. https://doi.org/10.3389/fnut.2022.1071276.

39. Cao, Y.; Xuan, B.; Peng, B.; Li, C.; Chai, X.; Tu, P. The Genus Lindera: A Source of Structurally Diverse Molecules Having Pharmacological Significance. *Phytochem. Rev.* **2016**, *15* (5), 869–906. https://doi.org/10.1007/s11101-015-9432-2.

40. Wen, S.-S.; Wang, Y.; Xu, J.-P.; Liu, Q.; Zhang, L.; Zheng, J.; Li, L.; Zhang, N.; Liu, X.; Xu, Y.-W.; Sun, Z.-L. Two New Sesquiterpenoid Lactone Derivatives from Lindera Aggregata. *Nat. Prod. Res.* **2022**, *36*(21), 5407–5415. https://doi.org/10.1080/14786419.2021.1939332.

41. Ho, H.K.; Chan, C.Y.; Hardy, K.D.; Chan, E.C.Y. Mechanism-Based Inactivation of CYP450 Enzymes: A Case Study of Lapatinib. *Drug Metab. Rev.* **2015**, *47*(1), 21–28. https://doi.org/10.3109/03602532.2014.1003648.

42. Wang, H.; Wang, K.; Mao, X.; Zhang, Q.; Yao, T.; Peng, Y.; Zheng, J. Mechanism-Based Inactivation of CYP2C9 by Linderane. *Xenobiotica* **2015**, *45* (12), 1037–1046. https://doi.org/10.3109/00498254.2015.1041002.

43. Wang, K.; Zhang, T.; Rao, J.; Peng, T.; Gao, Q.; Feng, X.; Qiu, F. Drug-Drug Interactions Induced by Linderane Based on Mechanism-Based Inactivation of CYP2C9 and the Molecular Mechanisms. *Bioorganic Chem.* **2022**, *118*, 105478. https://doi.org/10.1016/j.bioorg.2021.105478.

44. Dalli, M.; Bekkouch, O.; Azizi, S.; Azghar, A.; Gseyra, N.; Kim, B. Nigella Sativa L. Phytochemistry and Pharmacological Activities: A Review (2019–2021). *Biomolecules* **2021**, *12* (1), 20. https://doi.org/10.3390/biom12010020.

45. Malik, S.; Singh, A.; Negi, P.; Kapoor, V. K. Thymoquinone: A Small Molecule from Nature with High Therapeutic Potential. *Drug Discov. Today* **2021**, *26* (11), 2716–2725. https://doi.org/10.1016/j.drudis.2021.07.013

46. Muralidharan-Chari, V.; Kim, J.; Abuawad, A.; Naeem, M.; Cui, H.; Mousa, S. A. Thymoquinone Modulates Blood Coagulation in Vitro via Its Effects on Inflammatory and Coagulation Pathways. *Int. J. Mol. Sci.* **2016**, *17* (4), 474. https://doi.org/10.3390/ijms17040474.

47. Rukoyatkina, N.; Butt, E.; Subramanian, H.; Nikolaev, V. O.; Mindukshev, I.; Walter, U.; Gambaryan, S.; Benz, P. M. Protein Kinase A Activation by the Anti-Cancer Drugs ABT-737 and Thymoquinone Is Caspase-3-Dependent and Correlates with Platelet Inhibition and Apoptosis. *Cell Death Dis.* **2017**, *8* (6), e2898. https://doi.org/10.1038/cddis.2017.290.

48. Towhid, S. T.; Schmidt, E.-M.; Schmid, E.; Münzer, P.; Qadri, S. M.; Borst, O.; Lang, F. Thymoquinone-Induced Platelet Apoptosis. *J. Cell. Biochem.* **2011**, *112* (11), 3112–3121. https://doi.org/10.1002/jcb.23237.

49. Wang, Z.; Wang, X.; Wang, Z.; Lv, X.; Yin, H.; Li, W.; Li, W.; Jiang, L.; Liu, Y. Potential Herb-Drug Interaction Risk of Thymoquinone and Phenytoin. *Chem. Biol. Interact.* **2022**, *353*, 109801. https://doi.org/10.1016/j.cbi.2022.109801.

50. Elbarbry, F.; Ung, A.; Abdelkawy, K. Studying the Inhibitory Effect of Quercetin and Thymoquinone on Human Cytochrome P450 Enzyme Activities. *Pharmacogn. Mag.* **2018**, *13* (Suppl 4), S895–S899. https://doi.org/10.4103/0973-1296.224342

51. Albassam, A. A.; Ahad, A.; Alsultan, A.; Al-Jenoobi, F. I. Inhibition of Cytochrome P450 Enzymes by Thymoquinone in Human Liver Microsomes. *Saudi Pharm. J. SPJ Off. Publ. Saudi Pharm. Soc.* **2018**, *26* (5), 673–677. https://doi.org/10.1016/j.jsps.2018.02.024.

52. Al-Jenoobi, F. I.; Al-Thukair, A. A.; Abbas, F. A.; Ansari, M. J.; Alkharfy, K. M.; Al-Mohizea, A. M.; Al-Suwayeh, S. A.; Jamil, S. Effect of Black Seed on Dextromethorphan O- and N-Demethylation in Human Liver Microsomes and Healthy Human Subjects. *Drug Metab. Lett.* **2010**, *4* (1), 51–55. https://doi.org/10.2174/187231210790980435.