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# POTENTIATION OF WARFARIN ANTICOAGULATION BY TOPICAL HERBAL OIL: A CASE REPORT

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## ABSTRACT

*Warfarin is an effective oral anticoagulant for stroke prevention in atrial fibrillation and for the treatment of thromboembolic disorders. Despite its established effectiveness, warfarin has a narrow therapeutic window and is prone to drug, food, and herbal product interactions. Although interactions with oral drugs are well documented, data on interactions with topical agents remain scarce. This case report describes two instances of markedly elevated international normalised ratio (INR) associated with the use of a topical herbal oil. Two female patients on warfarin therapy presented to Hospital Kuala Lumpur with significantly elevated INR (>10) following the topical application of "Herbal Oil Y". Both patients were receiving warfarin to prevent stroke due to atrial fibrillation. The first patient, a 31-year-old woman, had initiated warfarin one week before admission. The second patient, a 69-year-old woman, had been taking warfarin for five years. Both patients denied recent dietary changes, over-the-counter medications, or oral herbal supplements. However, they reported applying Herbal Oil Y a day before admission. Warfarin induced over-anticoagulation was treated with intravenous vitamin K or prothrombin complex concentrate. Both patients were discharged in stable condition after close ward monitoring. These cases suggest a possible interaction between topically applied Herbal Oil Y and warfarin, likely due to the systemic absorption of active herbal constituents. Patients receiving warfarin therapy should be counselled on the potential risks associated with concomitant herbal product use, including topical preparations, to minimise adverse events.*

***Keywords:*** Warfarin, Herbal oil, Interaction, Over-anticoagulation, International normalised ratio

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## INTRODUCTION

Coumarins or vitamin K antagonists (VKAs) have been the mainstay of oral anticoagulant therapy for more than 50 years (Ansell *et al.* 2004). The efficacy of VKAs has been established in well-designed clinical trials for the prevention and treatment of venous thrombosis as well as for the prevention of thromboembolic complications associated with atrial fibrillation (AF) (Ansell *et al.* 2004; Kuruvilla and Gurk-Turner 2001).

Despite their established efficacy, pharmacotherapy with VKAs, such as warfarin, has always been challenging. In addition to having a narrow therapeutic index, warfarin does not exhibit a normal dose-response pattern. Warfarin is a highly protein-bound drug, and its involvement in cytochrome P450 (CYP) enzyme metabolism via CYP2C9, CYP1A2 and CYP3A4 makes it prone to interactions with drugs, food, and herbs (Leite *et al.* 2021). Warfarin exists as a racemic mixture of the S- and R-enantiomers. Since the S-enantiomer is more potent and primarily metabolised by CYP2C9, interactions with drugs, food and herbs affecting this pathway may be clinically significant (Di Minno *et al.* 2017).

Furthermore, warfarin is involved in the complex clotting cascade via the intrinsic and extrinsic pathways through its effects on vitamin K-dependent clotting factors II, VII, IX and X, as well as the anticoagulant proteins C and S (Adams and Bird 2009). Thus, pharmacodynamic (PD) interactions may occur with the use of medications such as non-steroidal anti-inflammatory drugs (NSAIDs) or herbs that inhibit platelet function and aggregation, thereby increasing the risk of bleeding (Mar *et al.* 2022; Di Minno *et al.* 2017).

The international normalised ratio (INR) is a test routinely performed to measure the anticoagulant effects of warfarin in terms of its effectiveness and safety. Randomised trials and observational studies support the use of an INR target of 2.0–3.0 to prevent ischaemic stroke in patients with AF (Hylek *et al.* 2003; Kleindorfer *et al.* 2021). Hence, the dose of warfarin is adjusted based on INR values to prevent thrombosis from a subtherapeutic INR of less than 2.0 or haemorrhagic complications from a supratherapeutic INR of more than 3.0 (Mar *et al.* 2022).

Although drug-drug interactions with warfarin are well-known and proven by published studies, the interactions between warfarin and topical agents remain largely unknown. The following cases are presented to explore the possibility of an interaction between warfarin and a topical herbal product known as “Herbal Oil Y”.

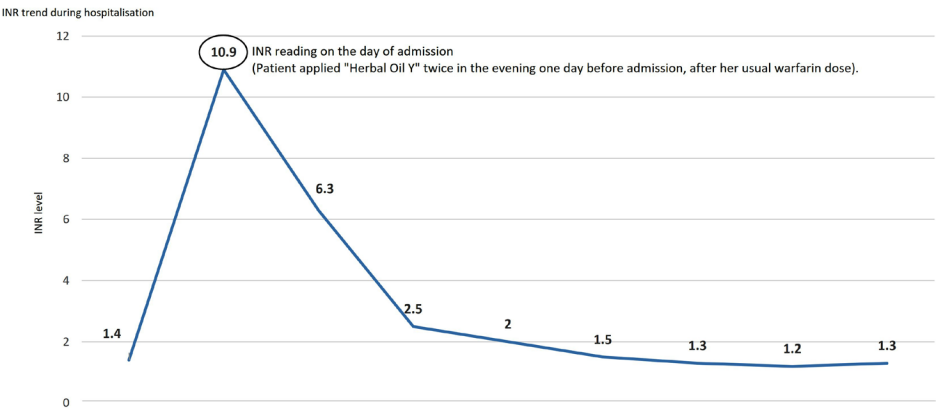
### Case Presentation

#### *Case 1*

A 31-year-old Malay woman presented to the emergency department (ED) with complaints of dyspnoea, palpitations and reduced effort tolerance for the past two days. The patient had underlying hyperthyroidism, dilated cardiomyopathy and AF. Her concomitant medications included carbimazole 20 mg once daily, spironolactone 12.5 mg once daily, bisoprolol 2.5 mg once daily, pantoprazole 40 mg once daily and warfarin 3.5 mg once daily. Warfarin 3 mg daily was initiated during a hospitalisation 8 days prior to the current admission for stroke prevention in AF (SPAF) with a target INR of 2.0–3.0. At the Warfarin Clinic follow-up visit 4 days before the current admission, her INR was subtherapeutic at 1.4, prompting a loading dose of warfarin 5 mg and an increase in the maintenance dose to 3.5 mg daily.

On the day of admission, patient was hypotensive (blood pressure 90/60mmHg) and tachycardic (heart rate 160 beats/min). Electrocardiogram (ECG) revealed fast AF, and the patient was given a loading dose of intravenous (IV) digoxin 0.5 mg. The diagnosis was

acute decompensated heart failure precipitated by fast AF. As the patient was on warfarin, routine INR monitoring revealed a markedly elevated value of 10.9, but no active bleeding was observed. Her thyroid function tests showed a thyroxine (T4) level of 5.07 pmoL/L and a thyroid stimulating hormone (TSH) level of 0.01 mIU/L; both readings were below the normal range. Carbimazole and warfarin were withheld, and a single dose of IV vitamin K 5 mg stat was administered. Repeat INR 5 days later was 1.5. Figure 1 shows the patient's INR trend during hospitalisation.




| Day of admission | 4 days before admission | Day 1 | Day 2 | Day 3 (post vitamin K) | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 |
|---|---|---|---|---|---|---|---|---|---|
| INR level | 1.4 | 10.9 | 6.3 | 2.5 | 2 | 1.5 | 1.3 | 1.2 | 1.3 |
| Warfarin dose | 3.5mg once daily | | warfarin was withheld | | | | 3mg once daily | | |

**Figure 1:** INR trend of case 1 patient.

Upon obtaining a further history, the patient denied taking any other traditional supplements or over-the-counter (OTC) medicines. She also denied any change in her warfarin dose, and her diet had remained consistent before hospitalisation. However, 1 day before hospital admission, she reported applying a topical product known as "Herbal Oil Y" twice over her abdomen. The patient was closely monitored in the ward and advised discontinuing applying the oil.

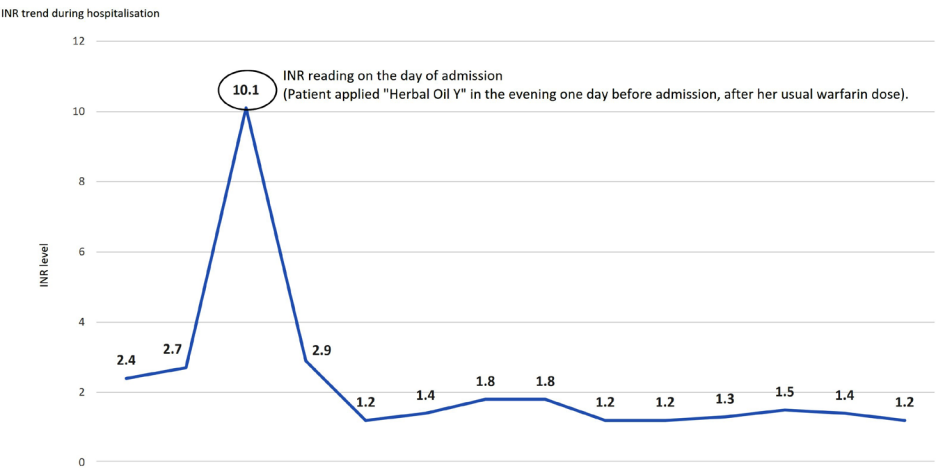
On day 6 of admission, the patient was restarted on a reduced dose of warfarin 3 mg daily when her INR was 1.3. On day 9 of admission, ultrasound imaging of her abdomen revealed no intra-abdominal collection. The patient was hospitalised for a total of 13 days and was discharged with the following medications; warfarin 3 mg once daily, carbimazole 10 mg once daily, pantoprazole 40 mg once daily, bisoprolol 3.75 mg once daily, and spironolactone 12.5 mg twice daily. She was scheduled for a follow-up visit at the Warfarin Clinic 3 days after discharge.

### *Case 2*

A 69-year-old Malay woman was brought to the ED with complaints of left-sided colicky abdominal pain, melaena and multiple enlarging bruises over her body that had persisted for 9 days. She also had extensive abdominal bruising, rectal impaction and melaenic stools. The patient had underlying diabetes mellitus, hypertension, AF, stage 4 chronic

kidney disease (CKD), gout and a history of right below knee amputation 4 years ago. She had been taking warfarin for SPAF for 5 years, with a current regimen of warfarin 3.5 mg daily from Monday to Friday and 3 mg daily on Saturday and Sunday. The patient's INR value during the last Warfarin Clinic visit 8 days before admission was 2.7. Her other concomitant medications included amlodipine 10 mg once daily, bisoprolol 3.75 mg once daily, allopurinol 100 mg once daily, ferrous fumarate 400 mg once daily and folic acid 5 mg once daily.

The patient was tachypnoeic (respiratory rate 24 breaths/min) and tachycardic (heart rate 116 beats/min). Blood tests revealed an elevated INR value of 10.1 and a low haemoglobin (Hb) level of 4.3 g/dL. She was diagnosed with hypovolaemic shock secondary to upper gastrointestinal bleeding precipitated by warfarin over-anticoagulation. Warfarin was withheld, and the patient was given one single dose of IV vitamin K 10 mg stat, followed by a single dose of IV prothrombin complex concentrate (PCC) 3,200 units (40 units/kg). The patient's INR value improved from 10.1 to 2.9, 1 hour post-PCC transfusion. Ultrasound imaging of her abdomen performed on day 2 of admission revealed a large subcutaneous collection at her anterior abdomen, which was likely a haematoma. Therefore, the patient was administered IV vitamin K 5 mg daily for 3 days, and a repeat INR on day 6 of admission was 1.2. Figure 2 shows her INR trend while in hospital.




| | 2 months before admission | 8 days before admission | Day 1 | Day 1 (post PCC) | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 12 | Day 19 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| INR level | 2.4 | 2.7 | 10.1 | 2.9 | 1.2 | 1.4 | 1.8 | 1.8 | 1.2 | 1.2 | 1.3 | 1.5 | 1.4 | 1.2 |
| Warfarin Dose | 2.5mg once daily (Mon - Fri) | | Warfarin was withheld | | | | | | | | | | | |
| | 3mg once daily (Sat - Sun) | | | | | | | | | | | | | |

**Figure 2:** INR trend of case 2 patient.

Upon obtaining a further history, the patient denied taking any traditional supplements or OTC medicines other than her prescribed medications. She also denied any change in her warfarin dose, and her diet intake had remained consistent before hospitalisation. However, the patient reported applying Herbal Oil Y to her abdomen one day before admission, after taking her usual dose of warfarin that same evening. Additionally,

the patient had been taking allopurinol tablet for the past six months, prescribed by her primary care physician for gout. Consequently, allopurinol was discontinued during the current hospital admission to minimise potential interacting factors.

The patient was hospitalised for 19 days, and the plan was to re-initiate warfarin at the outpatient clinic after discharge. She was counselled in the presence of her family members to avoid Herbal Oil Y in the future. She was discharged in a stable condition with pantoprazole 40 mg once daily, amlodipine 10 mg once daily, bisoprolol 2.5 mg once daily, ascorbic acid 100 mg once daily, ferrous fumarate 400 mg once daily and lactulose syrup 15 mL when needed.

## DISCUSSION

This case series highlight a possible interaction between warfarin and a topical herbal preparation, Herbal Oil Y, resulting in significantly elevated INR levels and clinical bleeding in one patient. While pharmacokinetic (PK) and PD interactions between warfarin and orally administered drugs or herbal supplements are well documented, data regarding topical herbal applications remain scarce (Leite *et al.* 2021; Talasaz *et al.* 2025).

### Clinical Presentation

Although both patients presented with supratherapeutic INR levels (>10) following the application of Herbal Oil Y, their clinical presentations differed significantly. Case 1 presented with symptoms of acute decompensated heart failure (dyspnoea, palpitations) precipitated with fast AR, and the elevated INR was an incidental finding without clinical bleeding. This may be attributed to her younger age (31 years old) and absence of significant comorbidities. Conversely, case 2 presented with symptoms of active bleeding, such as melaena and extensive bruises. This patient was likely more susceptible due to her advanced age (69 years old) and stage 4 CKD. CKD is associated with an increased risk of baseline bleeding due to uraemic platelet dysfunction and altered warfarin protein binding (Adams and Bird 2009; Limdi *et al*. 2009). Therefore, while the interaction occurred in both cases, the clinical consequences were more severe in older patients with multiple comorbidities.

### Analysis of Herbal Components and Their Mechanisms

Natural or essential oils derived from plants, when applied topically, can not only be absorbed but may also compromise the integrity of the dermal barrier and enhance the penetration of other chemicals or substances (Nielsen 2006). Pharmacological principles of herbal medicines often involve multiple active components and target sites. Consequently, the potential of drug-herbs interactions may frequently occur, resulting in adverse effects and even fatal outcomes, particularly with drugs that have a narrow therapeutic window, such as warfarin (Lin and Lu 2001).

Herbal Oil Y is a traditional preparation easily purchased OTC. It is generally used as a topical product, externally applied to relieve abdominal bloating and alleviate minor pain through its cooling sensation. According to the product insert, Herbal Oil Y contains peppermint oil (36% w/v), clove oil (2.6% w/v), menthol (1.6% w/v), nutmeg oil (0.6% w/v), borneol (1% w/v), cortex cinnamon (1% w/v), resina calamus draco (1% w/v) and light liquid paraffin (1% w/v).

Peppermint oil, the primary constituent, is a volatile oil obtained from the plant *Mentha piperita* (Nair 2001). Although systemic absorption after dermal application is erratic, studies have shown that peppermint oil can enhance the transdermal penetration of topical medicines by reducing skin integrity (European Medicines Agency (EMA) Committee on Herbal Medicinal Products 2019; Williamson, Driver and Baxter 2009). Herbal Oil Y contains peppermint oil at 360 mg/mL. In vitro, peppermint oil at concentrations 20–500 mcg/mL has been reported to moderately inhibit the activity of CYP2C8, CYP2C9, CYP2C19 and CYP2D6 (Williamson, Driver and Baxter 2009; Unger and Frank 2004). Since CYP2C9 is the primary isoenzyme responsible for metabolising S-warfarin (the more potent enantiomer), its inhibition may lead to the accumulation of warfarin and an exaggerated anticoagulant effect (Nutescu *et al.* 2006). However, the clinical relevance of in vitro inhibition for systemic exposures achievable after topical application remains uncertain.

Both clove oil, extracted from the dried flower buds of *Syzygium aromaticum* (Haro-González *et al.* 2021), and *Cinnamoni cortex* (the bark of *Cinnamomum verum)* contain eugenol as their primary constituent (Committee for Veterinary Medicinal Products 2000). Eugenol is a potent CYP2C9 inhibitor (Nutescu *et al.* 2006; Cochrane 2015), a property also reported for components of nutmeg oil and borneol-containing preparations (Cochrane 2015). Although specific data on clinically relevant inhibitory concentrations are limited, the multiple constituents in Herbal Oil Y could contribute to reduced VKA metabolism if sufficient systemic exposure is achieved.

Beyond metabolic inhibition, these components may have PD interactions with warfarin. Eugenol exhibits antithrombotic activity by inhibiting platelet aggregation and thromboxane synthesis (Saeed and Gilani 1994; Srivastava 1993). Similarly, resina calamus draco (*Draconis Resina* or Dragon's blood), another component of Herbal Oil Y, contains a flavonoid (2S-5-methoxy-6-methylflavan-7-ol) that has demonstrated antiplatelet activity comparable to eugenol (Tsai *et al.* 1998). Such pharmacodynamic interactions can interfere with clotting mechanisms, decrease blood coagulation and prolong bleeding time (Liao and Li 1997).

Menthol, another constituent of Herbal Oil Y, is widely used as a topical analgesic (Pergolizzi *et al.* 2018). It has been shown to inhibit CYP2A6 and CYP2A13 (Kramlinger Von Weymarn and Murphy 2012; Zehetner, Höferl and Buchbauer 2019), but these enzymes are not involved in warfarin metabolism. Accordingly, interactions between topical menthol products and warfarin have not been reported to date. Hence, they are unlikely to account for the observed changes in INR.

**Clinical Implications**

Notably, our literature review did not identify any controlled human or animal in vivo studies that directly examine the effects of peppermint oil, eugenol, nutmeg oil, or borneol on warfarin PK, INR, or bleeding outcomes. Information on these components is predominantly derived from in vitro enzyme assays and general herb-warfarin interaction reviews, thus providing indirect mechanistic support for a causal link.

Nevertheless, several clinical features support the possible contribution of Herbal Oil Y to the supratherapeutic INR values observed. In both patients, there were no recent changes in dietary intake, prescription or OTC medications, or oral herbal supplements prior to hospitalisation. The marked INR elevation (>10) that developed within 24 hours of Herbal Oil Y application suggests that intensive application of a multicomponent essential oil

preparation may achieve sufficient systemic exposure to acutely affect warfarin metabolism. This is particularly relevant when the herbal oil is applied to large surface areas, as with abdominal application in both patients.

### Alternative Causes

Additionally, it is crucial to exclude other factors, including concomitant medications and underlying disease states. Case 1 was treated with carbimazole for hyperthyroidism. While carbimazole may act as a VKA, potentially increasing the anticoagulant effect of warfarin (Amdipharm UK Limited 2024), thyroid status can also impact warfarin sensitivity. Elevated thyroid hormone levels (hyperthyroidism) potentiate the anticoagulant effect of warfarin by accelerating the degradation of vitamin K-dependent clotting factors and decreasing warfarin protein binding (Feely *et al.* 1981; Kellett *et al.* 1986).

However, effective carbimazole therapy shifts thyroid function towards euthyroid or hypothyroidism, thereby slowing the metabolism of vitamin K-dependent clotting factors (Howard-Thompson *et al.* 2014). This physiological effect was clinical evident in the patient's INR value which was subtherapeutic (1.4), just 4 days before admission, requiring a dose increase. Given her low T4 level (5.07 pmol/L) and absence of carbimazole dose changes, it is unlikely that her thyroid status contributed to the acute INR elevation to above 10, supporting the role of Herbal Oil Y as a precipitating factor instead.

In case 2, the potential interaction with warfarin involves her underlying CKD and concomitant medications, including allopurinol and amlodipine. Clinical reports have described an increase in the anticoagulant effect of VKAs with the concurrent use of allopurinol (Self, Evans and Ferguson 1975, Pond *et al.* 1975). However, in this case, the patient had been on stable dose of allopurinol for six months. Her two most recent INR readings during Warfarin Clinic follow-up visits, 5 months and 2 months before admission, were 2.8 and 2.4, respectively, both within the target range. The lack of recent allopurinol dosage adjustments and the prior stable INR values make allopurinol an unlikely cause for the acute INR elevation.

Similarly, the patient was taking amlodipine, which is a weak inhibitor of CYP3A4 (Krasulova, Holas and Anzenbacher 2017). CYP3A4 is responsible for metabolism of the less potent R-enantiomer, hence interactions involving CYP3A4 inhibition are generally considered clinically less significant than those affecting CYP2C9 (Mar *et al.* 2022; Di Minno *et al.* 2017). Given the patient's long-term stability on amlodipine before admission, amlodipine is unlikely to have precipitated such a drastic rise in INR. Moreover, her underlying CKD may have contributed to the clinical bleeding but is unlikely to have caused the sudden INR fluctuation. Therefore, the distinct timing of Herbal Oil Y application correlates most strongly with the acute INR elevation.

## CONCLUSION

To the best of our knowledge, no prior study has documented an interaction between topical Herbal Oil Y and warfarin. Nevertheless, majority constituents in Herbal Oil Y are known to inhibit warfarin metabolism, raising the possibility of potentiated anticoagulant effects. We therefore postulate that systemic absorption of the topically applied Herbal Oil Y contributed to the enhanced anticoagulant response observed in both patients.

In summary, although definitive causality cannot be established from these two cases, the temporal association, pharmacological plausibility, and absence of alternative explanations for the marked INR elevation suggest that topical multicomponent essential oil preparations, such as Herbal Oil Y, may pose a risk for warfarin over-anticoagulation in susceptible individuals. Patients taking warfarin should be cautioned against intensive use of topical herbal products until more robust *in vivo* evidence becomes available.

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## REFERENCES

ADAMS, R. L. & BIRD, R. J. (2009) Review article: Coagulation cascade and therapeutics update: relevance to nephrology. Part 1: Overview of coagulation, thrombophilias and history of anticoagulants, *Nephrology (Carlton)*, 14(5): 462–470. https://doi.org/10.1111/j.1440-1797.2009.01128.x

AMDIPHARM UK LIMITED (2024) Carbimazole (Neomercazole) [Product labelling], London, United Kingdom: Amdipharm UK Limited.

ANSELL, J., HIRSH, J., POLLER, L., BUSSEY, H. *et al*. (2004) The pharmacology and management of the vitamin K antagonists: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy, *Chest*, 126(Supp. 3): 204s–233s. https://doi.org/10.1378/chest.126.3_suppl.204S

COCHRANE, M. L. (2015) *Inhibition of cytochrome P450 2C9 by essential oils*, The University of North Carolina at Greensboro.

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS. (2000) The European Agency for the Evaluation of Medicinal Products Veterinary Medicines and Information Technology Unit Summary report on *Cinnamomi ceylanici cortex*, https://www.ema.europa.eu/en/documents/mrl-report/cinnamomi-ceylanici-cortex-summary-report-committee-veterinary-medicinal-products_en.pdf. (6 September 2022).

DI MINNO, A., FRIGERIO, B., SPADARELLA, G., RAVANI, A. *et al*. (2017) Old and new oral anticoagulants: Food, herbal medicines and drug interactions, *Blood Reviews*, 31(4), 193–203. https://doi.org/10.1016/j.blre.2017.02.001

EUROPEAN MEDICINES AGENCY (EMA) COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC). (2019) European Union herbal monograph on Mentha x piperita L. aetheroleum, https://www.ema.europa.eu/en/documents/herbal-monograph/draft-european-union-herbal-monograph-mentha-x-piperita-l-aetheroleum-revision-1_en.pdf. (5 Sep 2022).

FEELY, J., STEVENSON, I. H. & CROOKS, J. (1981) Altered plasma protein binding of drugs in thyroid disease, *Clinical Pharmacokinetics*, 6: 298–305. https://doi.org/10.2165/00003088-198106040-00004

HARO-GONZALEZ, J. N., CASTILLO-HERRERA, G. A., MARTINEZ-VELAZQUEZ, M. & ESPINOSA-ANDREWS, H. (2021) Clove Essential Oil (Syzygium aromaticum L. Myrtaceae): Extraction, chemical composition, food applications, and essential bioactivity for human health, *Molecules*, 26(21): 6387. https://doi.org/10.3390/molecules26216387

HOWARD-THOMPSON, A., LUCKEY, A., GEORGE, C., CHOBY, B. A. *et al.* (2014) Graves' disease and treatment effects on warfarin anticoagulation, *Case Reports in Medicine*, 2014: 292468. https://doi.org/10.1155/2014/292468

HYLEK, E. M., GO, A. S., CHANG, Y., JENSVOLD, N. G. *et al.* (2003) Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation, *New England Journal of Medicine*, 349(11)**,** 1019–1026. https://doi.org/10.1056/NEJMoa022913

KELLETT, H. A., SAWERS, J. S., BOULTON, F. E., CHOLERTON, S. *et al.* (1986) Problems of anticoagulation with warfarin in hyperthyroidism. *The Quarterly Journal of Medicine*, 58(225): 43–51.

KLEINDORFER, D. O., TOWFIGHI, A., CHATURVEDI, S., COCKROFT, K. M. *et al.* (2021) 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline from the American Heart Association/American Stroke Association. *Stroke*, 52(7): e364–e467. https://doi.org/10.1161/STR.0000000000000375

KRAMLINGER, V. M., VON WEYMARN, L. B. & MURPHY, S. E. (2012) Inhibition and inactivation of cytochrome P450 2A6 and cytochrome P450 2A13 by menthofuran, β-nicotyrine and menthol, *Chemico-Biological Interactions*, 197(2–3)**:** 87–92. https://doi.org/10.1016/j.cbi.2012.03.009

KRASULOVA, K., HOLAS, O. & ANZENBACHER, P. (2017) Influence of amlodipine enantiomers on human microsomal cytochromes P450: Stereoselective time-dependent inhibition of CYP3A enzyme activity, *Molecules*, 22(11): 1879. https://doi.org/10.3390/molecules22111879

KURUVILLA, M. & GURK-TURNER, C. (2001) A review of warfarin dosing and monitoring. *Baylor University Medical Center Proceedings: The peer-reviewed journal of Baylor Scott & White Health*, 14(3)**,** 305–306. https://doi.org/10.1080/08998280.2001.11927781

LEITE, P. M., MARTINS, M. A. P., CARVALHO, M. D. G. & CASTILHO, R. O. (2021) Mechanisms and interactions in concomitant use of herbs and warfarin therapy: An updated review, *Biomedicine & Pharmacotherapy*, 143: 112103. https://doi.org/10.1016/j.biopha.2021.112103

LIAO, F. L. & LI, B. (1997) Inhibition of shear-induced platelet aggregation by Chinese herbal medicines, *Clinical Hemorheology and Microcirculation*, 17(4)**,** 315–318.

LIMDI, N. A., BEASLEY, T. M., BAIRD, M. F., GOLDSTEIN, J. A. *et al.* (2009) Kidney function influences warfarin responsiveness and hemorrhagic complications, *Journal of the American Society of Nephrology*, 20(4): 912–921. https://doi.org/10.1681/ASN.2008070802

LIN, J. H. & LU, A. Y. (2001) Interindividual variability in inhibition and induction of cytochrome P450 enzymes, *Annual Review Pharmacolology and Toxicology*, 41: 535–567. https://doi .org/10.1146/annurev.pharmtox.41.1.535

MAR, P. L., GOPINATHANNAIR, R., GENGLER, B. E., CHUNG, M. K. *et al*. (2022) Drug interactions affecting oral anticoagulant use, *Circulation: Arrhythmia and Electrophysiology,* 15(6). https://doi.org/10.1161/CIRCEP.121.007956

NAIR, B. (2001) Final report on the safety assessment of Mentha Piperita (Peppermint) Oil, Mentha Piperita (Peppermint) Leaf Extract, Mentha Piperita (Peppermint) Leaf, and Mentha Piperita (Peppermint) Leaf Water, *International Journal of Toxicology*, 20 (Suppl. 3)**:** 61–73. https://doi.org/10.1080/10915810152902592

NIELSEN, J. B. (2006) Natural oils affect the human skin integrity and the percutaneous penetration of benzoic acid dose-dependently, *Basic & Clinical Pharmacology & Toxicology*, 98(6)**,** 575–581. https://doi.org/10.1111/j.1742-7843.2006.pto_388.x

NUTESCU, E. A., SHAPIRO, N. L., IBRAHIM, S. & WEST, P. (2006) Warfarin and its interactions with foods, herbs and other dietary supplements, *Expert Opinion on Drug Safety*, 5(3): 433–51. https://doi.org/10.1517/14740338.5.3.433

PERGOLIZZI, J. V., JR., TAYLOR, R., JR., LEQUANG, J. A. & RAFFA, R. B. (2018) The role and mechanism of action of menthol in topical analgesic products. *Journal of Clinical Pharmacy and Therapeutics*, 43(3): 313–319. https://doi.org/10.1111/jcpt.12679

POND, S. M., GRAHAM, G. G., WADE, D. N. & SUDLOW, G. (1975) The effects of allopurinol and clofibrate on the elimination of coumarin anticoagulants in man, *Australian and New Zealand Journal of Medicine*, 5(4): 324–328.

SAEED, S. A. & GILANI, A. H. (1994) Antithrombotic activity of clove oil, *The Journal of the Pakistan Medical Association*, 44(5): 112–115.

SELF, T. H., EVANS, W. E. & FERGUSON, T. (1975) Letter: Drug enhancement of warfarin activity, *The Lancet*, 306(7934): 557–558. https://doi.org/10.1016/s0140-6736(75)90937-x

SRIVASTAVA, K. C. (1993) Antiplatelet principles from a food spice clove (Syzygium aromaticum L), *Prostaglandins Leukot Essent Fatty Acids*, 48(5)**,** 363–372. https://doi.org/ 10.1016/0952-3278(93)90116-e

TALASAZ, A. H., MCGONAGLE, B., HAJIQASEMI, M., GHELICHKHAN, Z. A. *et al*. (2025) Pharmacokinetic and pharmacodynamic interactions between food or herbal products and oral anticoagulants: Evidence review, practical recommendations, and knowledge gaps, *Semin Thromb Hemost*, 51(05): 560–571. https://doi.org/10.1055/s-0044-1790258.

TSAI, W. J., HSIEH, H. T., CHEN, C. C., KUO, Y. C. *et al.* (1998) Characterization of the antiplatelet effects of (2S)-5-methoxy-6-methylflavan-7-ol from Draconis Resina, *European Journal of Pharmacology*, 346(1): 103–110. https://doi.org/10.1016/S0014-2999(98)00011-9

UNGER, M. & FRANK, A. (2004) Simultaneous determination of the inhibitory potency of herbal extracts on the activity of six major cytochrome P450 enzymes using liquid chromatography/mass spectrometry and automated online extraction, *Rapid Communications Mass Spectrometry,* 18(19): 2273–2281. https://doi.org/10.1002/rcm.1621

WILLIAMSON, E., DRIVER, S. & BAXTER, K. (2009) *Stockley's Herbal Medicines Interactions: A Guide to the Interactions of Herbal Medicines*, 2nd edition, pp. 320 (London: Pharmaceutical Press).

ZEHETNER, P., HÖFERL, M. & BUCHBAUER, G. (2019) Essential oil components and cytochrome P450 enzymes: A review, *Flavour and Fragrance Journal*, 34(4): 223–240. https://doi.org/10.1002/ffj.3496