Interaction of Warfarin with Herbs Based on Pharmacokinetic and Pharmacodynamic Parameters

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ABSTRACT

Warfarin is an oral anticoagulant that has been widely used and has strong efficacy, but the use of warfarin is still a concern because of its narrow therapeutic index which cause interactions when co-administration with drugs, herbs or food. This interaction can affect the pharmacokinetics and pharmacodynamics of warfarin and the most fatal effect from warfarin interactions is bleeding. In this review article data on warfarin-herbs interactions were collected based on pharmacokinetic parameters (AUC₀–∞, Cₘₐₓ, T₁/₂, Cl/F, and V/F), while pharmacodynamic parameters (International normalized ratio (INR), platelet aggregation, AUC INR and Protombine Time). As a result some herbs had significant interactions with warfarin. Herbs that affect warfarin pharmacokinetic were Danshen gegen, echinacea, St. John's wort and caffeine and herbs that affect pharmacodynamic were policosanol, Ginkgo biloba, cranberry, St. John's wort, ginseng, pomegranate, Psidium guajava and curcumin, so co-administration warfarin with herbs need to be considered.

Keywords: Warfarin, Interactions, Herbs, Pharmacokinetics, Pharmacodynamics

1. Introduction

Warfarin is an oral anticoagulant that had been widely used since 1954 and prescribed for decades (1). Warfarin is used to prevent thromboembolic complications in a patient with various cardiovascular diseases including atrial fibrillation and thrombosis (2). The anticoagulation effect of warfarin is achieved by inhibit the formation cycle of vitamin K in the liver. It inhibits vitamin K epoxide reductase (VKOR) that very important in the formation of factors VII and IX in blood clotting (3). Although warfarin has strong efficacy, the use of warfarin is still a concern because of its narrow therapeutic window, it cause an interaction when co-administration with drugs, herbs, or foods.

Drug-drug interaction occurs every time the effects of the drug are modified by the presence of other drugs which causes therapeutic failure, toxicity, or serious complication (4). Warfarin is included in the top ten of drugs with severe side effects in 2019 (5). Based on a report in the United States, about 58% patients who take warfarin, they also take herbal medicines to improve their health condition (6,7). While there is 34 warfarin interaction from 133 cases of herb-drug interaction (8), because of that warfarin is one of the most frequently studied drug-related to its interactions. This interaction can affect the pharmacokinetic and pharmacodynamic of warfarin, and the most fatal effect by warfarin interaction is bleeding (9).
CYP2C19, while S-warfarin mainly metabolized by CYP2C9 (10, 11). Many studies have shown that warfarin interactions are mediated by CYP enzymes and protein plasma binding (12). The herbs can influence the enzymes and affect pharmacokinetic and pharmacodynamic of warfarin.

The herbs influence the metabolism enzyme of warfarin by inhibition or induction. A few herbs have been reported inhibit CYP2C9 enzyme including Harpagoptytum procumbens, Trifolium pratense (13), Citrus paradise (14), Serenoa repens (15), Glycine max (16), Angelica sinensis (17) while Allium sativum (18), Cannabis sativa (19) are reported induction CYP2C9.

Therefore it is necessary to gather information related to the interaction of warfarin with herbs based on pharmacokinetic and pharmacodynamics parameters, so the administration of warfarin therapy to patients who take certain herbal medicines can be more controlled, and reduce the side effects. This article will gather the information related to the interaction of warfarin with herbs based on its pharmacokinetic and pharmacodynamics parameters.

2. Methodology

In this review article, literature was collected from the internet through google scholar, Elsevier, Pubmed, using the keywords “warfarin”, “herb-drug interaction”, “interaction of warfarin”, “the pharmacokinetics of warfarin”, “pharmacokinetic drug interaction”, “pharmacodynamics interaction”, “pharmacodynamics of warfarin”. The data of warfarin interaction with some herbs were obtained based on the result of previous studies and we do further searches from the relevant references. Inclusion criteria are articles which have pharmacokinetic parameters, pharmacodynamic parameters, publication year > 2000, and articles that have references on warfarin, herbs, and drug interactions. The number of literature that has been collected was 145 articles, but only 65 articles included based on the inclusion criteria. It is illustrated by Figure 1.

Figure 1. Flow Chart Of the Literature Review
3. Discussion

There are two classifications of drug interactions: pharmacokinetic interactions and pharmacodynamic interactions. Pharmacokinetic interaction is associated with absorption, distribution, metabolism, and excretion. It can change drug concentration in blood. Pharmacodynamic interaction is related to drug effects, it is classified into three groups such as direct effect at receptor function, interference with a biological or physiological control process and additive/opposed pharmacological effect (20). Pharmacokinetic and pharmacodynamic interactions occur due to the presence of other substances that affect the drug, for example when using herbs simultaneously, the active ingredients of these herbs cause the interactions. This interaction can be seen from changes in pharmacokinetic parameters and pharmacodynamic parameters.

The pharmacokinetic parameters are area under curve \(e^{-\infty} \) (AUC\( e^{-\infty} \)) is area under the plasma concentration time in zero to infinity. \(C_{\text{max}}\) is the maximum concentration of drug in plasma. \(T_{\text{max}}\) is the maximum time to reach maximum plasma concentration. \(T_{1/2}\) is time required for drug to decline by half. Clearance (Cl/F) is the total clearance of drug after oral administration. Volume distribution (V/F) is the volume of distribution of drug after non-intravenous administration. Mean residence time (MRT). Fu is fraction of unbound drug in plasma (21). The pharmacodynamic parameters for warfarin are international normalized ratio (INR), AUC of INR, platelet aggregation, and protombine time (PT). PT is the time for blood to clot (22). This article has summarized the pharmacokinetic interaction of warfarin with herbs based on pharmacokinetic parameters in Table 1 and pharmacodynamic parameters in Table 2.

3.1 Danshen gegen

Based on of Zhou et al (23) extract of Danshen gegen (DG) was given to rats after warfarin administration for 5 days show influence on the pharmacokinetic parameters, such as \(C_{\text{max}}\), AUC \(0-\infty\) and \(T_{\text{max}}\). For R-warfarin, there was a decrease in the \(C_{\text{max}}\) from 1.03 mg/ml to 0.52 mg/ml, a decrease in the AUC from 13.09 mg/ml to 6.56 mg/ml, also decrease in \(T_{1/2}\) from 19.74 minutes to 10.98 minutes. For S-warfarin, there was a decrease in \(C_{\text{max}}\) from 1.44 mg/ml to 0.93 mg/ml, whereas for AUC \(0-\infty\) and \(T_{1/2}\) was not significantly different (Table 1).

In conclusion based on Table 1 (23) co-administration of DG extract with warfarin influence the pharmacokinetic parameters of warfarin in rats. It is caused by DG extract's active substances, such as pueraain (1986.0mg/100mg), salvianolic acid B (2048.3mg/100mg), daidzein (122.5 mg/100 mg), daidzin (190.9 mg /100 mg), protocatechouic aldehyde (117.3 mg/100 mg), and the hydrophobic components such as tanshinones (31).

The interaction between DG extract and warfarin is caused by the interaction of DG extract's active substance with cytochrome P450 (CYP450) (32). Tanshinones inhibit CYP3A4 (33). The results of studies on rats, Danshen gegen extract induces CYP1A2 activity around 60% (34), while on the other side according to Lin (34) tanshinone II A inhibits CYP1A2 (35). Component of Danshen gegen has been analyzed by clinical studies, a sequential studies on this enzyme show that CYP3A and CYP1A1 are induced by Danshen gegen (8). These findings indicate that there are potential interactions for drugs that are substrates for CYP3A4 or CYP1A2 when given together with Danshen gegen. As we know that the main metabolism of warfarin occurs in the liver by CYP2C9, CYP1A2, and CYP3A4, so the use of warfarin and Danshen gegen simultaneously needs to be reconsidered.

3.2 Policosanol and Echinacea

Echinacea is one of the herbal medicines that used as immunostimulants from Echinacea purpurea and Echinacea angustifolia (36). Policosanol is a complex mixture of alcohol obtained by extracting the Saccharum officinarum (37). Policosanol has been reported to reduce cholesterol levels (38), and can be used in patients with cardiovascular disease who receive warfarin therapy.

Administration of 25 mg warfarin to healthy volunteers simultaneously with echinacea (a mixture of 600 mg Echinacea angustifolia and 675 mg of Echinacea purpurea which is standardized with 5.75 mg alkamide per tablet), and policosanol
**Table 1. Pharmacokinetic Interaction of Warfarin with Herbs**

<table>
<thead>
<tr>
<th>No</th>
<th>Herb</th>
<th>Phase</th>
<th>Pharmacokinetic Parameters</th>
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<tr>
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<td>AUC (_{0-\infty}) (µg mL/h)</td>
<td>Cmax (µg/mL)</td>
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<td>gegen</td>
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<td></td>
<td>(Silvia)</td>
<td>S-warfarin</td>
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<td>1.03</td>
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<tr>
<td></td>
<td>Miltiorrhiza</td>
<td>S-warfarin + S.miltiorrhiza</td>
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<td>49</td>
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<td>R-warfarin</td>
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<td>R-warfarin</td>
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<td>1.7</td>
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<td>102.2</td>
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<td>R-warfarin + Ginger</td>
<td>102.6</td>
<td>1.7</td>
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<td>108.1</td>
<td>1.89</td>
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<td>Warfarin + Elegiac Acid</td>
<td>131.66</td>
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<td>Warfarin + Guava Leaves</td>
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<td>Warfarin</td>
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<tr>
<td></td>
<td></td>
<td>Warfarin + Curcumin 50 mg/kg</td>
<td>16.34</td>
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<tr>
<td></td>
<td></td>
<td>Warfarin + Curcumin 100 mg/kg</td>
<td>26.64</td>
<td>1.71</td>
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<tr>
<td>8</td>
<td>Caffeine</td>
<td>Warfarin</td>
<td>109.3</td>
<td>1.9</td>
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<tr>
<td></td>
<td></td>
<td>Warfarin + Caffeine</td>
<td>147.2</td>
<td>1.9</td>
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tablet 10 mg 2 times a day for 2 weeks show that echinacea increase the total clearance of S-warfarin but has no effect on R-warfarin. Administration of policosanol has no significant effect on the pharmacokinetic and pharmacodynamic parameters of warfarin (Table 1) (24).

Echinacea tablets contain more than 1% phenolic compound (caftaric acid, chlorogenic acid, echinacoside, and chichoric acid) as well as alkamides (2-ena and 2.4 dienes) (39). In Abdul study (24) tablets were used with the same content as the formulation in the study of Gorski et al (39). There was no effect of policosanol in pharmacokinetic of warfarin (39), so it could be linked to the cause of the absence of pharmacokinetic changes. Policosanol has been reported reduce blood cholesterol levels at a dose of 20 mg per day (40), but the results of Abdul (24) did not show any significant changes in platelet aggregation after being given policosanol 20 mg for 2 weeks (24). Other study reported no blood clotting factors after 8 weeks of treatment with policosanol 10 mg per day in cholesterol patients (41). Also, there is no significant relationship between the CYP2C9 or VKORC1 gene (40,41). The relatively small number of samples can influence the interpretation of the results. Although the results of Abdul et al (24) show that the use of warfarin together with policosanol and echinacea did not provide a significant interaction, the use of this substance needs to be maintained continuously.

3.3 Ginkgo and Ginger

Jiang et al (25) show there was no significant changes on pharmacokinetic and pharmacodynamics parameters of S-warfarin and R-warfarin in healthy volunteers (Table 1 and Table 2). It similar with Kumar (43) on administration of ginkgo with warfarin from international normalized ratio (INR) in patients consuming 100 mg of ginkgo extract daily for 4 weeks, it showed that ginkgo did not affect the warfarin (44).

Table 1 showed the level of urine excretion was not change after administratation of ginkgo and ginger which means that these two herbs did not affect CYP2C9 activity. When 60 mg of ginkgo extract was given 4 times daily for 28 days to healthy volunteers, there was no activity in CYP3A4, CYP1A2, CYP2E1, or CYP2D6. Although there are no interactions, the content of ginkgo has been reported to inhibit and induce cytochrome P450(43,44). In vitro studies the use of different doses of ginkgo, for example, EgB 761 extract contain less than 5ppm ginkgolide acid affect the activity of CYP (47).
Ginkgolides from ginkgo can inhibit platelet activating factor (48). However, there is also evidence that ginkgo did not affect adenosine diphosphate or platelet aggregation (49). Ginkgo also did not provide platelet or coagulation activity at doses of 120, 240 and 480 mg per day given for 14 days in healthy volunteers (46) which is in line with the results of Jiang et al (25).

3.4 Cranberry

Based on the results of Abdul et al (26) find that cranberry did not have a significant effect on warfarin (Table 1). Based on the pharmacodynamic parameters of warfarin after cranberry juice administration, there was a significant increase in the average value of AUC INR by 30% (Table 2) and it influences the platelet aggregation. It also supported by the results of Greenblatt et al (50) the activity of CYP2C9 did not affected by cranberry. Lilja et al (51) also examined the administration of cranberry juice for 5 days with warfarin, there was no significant change from AUC of S-warfarin.

However, the results of pharmacodynamic interactions of cranberry is different from Li et al (52) and Ansell et al (53), they found no significant changes in the warfarin response, but the volunteer by Li et al only 7 patients and Ansell (53) only 14 patients. Lilja et al (51) concluded the absence of pharmacodynamic interactions because of the dose of 10 mg with cranberry juice administration for only 7 days. According to Hamann et al (54) based on case reports, there is a change in the INR after administration of cranberry juice, it can be detected with a longer period and use a high dose of warfarin like 56 mg per week. From Abdul (26) we can conclude that the administration of cranberry for 2 weeks increased warfarin sensitivity to healthy volunteers, but did not have a pharmacokinetic effect, so the monitoring is needed regarding the use of warfarin with cranberry.

3.5 St John’s wort and Ginseng

12 healthy volunteers were given 25 mg of warfarin together with St. John's wort for 14 days and 7 days of ginseng (27). Co-administration of St. John’s wort with warfarin at the recommended dose can increase the clearance of warfarin enantiomers and decrease the pharmacodynamic effects of warfarin. The administration of ginseng did not provide a significant difference to the pharmacokinetic parameters of warfarin (27).

There were significant differences of the AUC, T1/2, and Cl/F of R-warfarin and S-warfarin by St. John's wort. While pharmacodynamic parameters show significant differences after the administration of warfarin with St. John's wort (Table 2). However, when warfarin was given with ginseng there is no significant differences, there was still a change in the value of INR and platelet aggregation (27).

St John’s wort inhibits the activity of CYP2C9, CYP2D6, and CYP3A4 (55), but St John’s wort also induction CYP1A2, CYP2E1, and CYP3A4 (56). The test of healthy volunteers for 14 days St John’s wort induce CYP3A4 activity in the liver (56). This effect due to the existence of the pregnane X receptor (PXR) (57). The influence of St. John's wort in the activity of the CYP450 enzyme is the cause of the pharmacokinetic changes from warfarin because these enzymes play a role in warfarin metabolism (27).

It can be concluded that St. John’s wort has potential action with drugs whose metabolism is influenced by CYP2C9 and CYP3A4 substrates. The result of Jiang (27) can be evidence to support recommendations for monitoring the INR on patients when warfarin co-administration with drugs.

3.6 Pomegranate Peel Extract and Guava Leaves Extract

The results of Alnaqeeb et al (28) on administration of warfarin 0.5 mg/kg with 250 mg/kg guava leaf extract and 100 mg/kg pomegranate peel extract for 5 days showed that it increased the value of protombine time (PT) and INR warfarin (Table 2). Elagitanins and elagic acid in pomegranate peel has a strong action in decreasing platelet aggregation in human plasma (58). It causes an increase in PT after pomegranate peel extract is given. While the effect of guava leaf extract on the PT and INR was also related to the antiplatelet activity of the flavonoids contained in it, especially quercetin which potentially increase the risk of bleeding (59).

The study pharmacokinetic interaction of warfarin showed that there was no significant
effect of pomegranate peel extract on plasma warfarin concentration, this could be related to the low of elagitanin content in the extract. Although there was an increase in $C_{\text{max}}$ because the elagic acid and elagitanin could inhibit CYP3A and P-glycoprotein (60).

Pharmacokinetic interactions between warfarin and guava leaf extract significantly increase $C_{\text{max}}$ (Table 1), and significantly change AUC and Cl. It is caused by quercetin which can inhibit the activity of CYP2C9, CYP2C8 and CYP3A4 (61,62). It can be concluded that the administration of warfarin simultaneously with pomegranate peel extract and guava leaf extract have pharmacokinetic and pharmacodynamic interaction.

3.7 Curcumin

Curcumin is an active ingredient of *Curcuma longa* that has been widely used as a food ingredient, has antioxidant activity, and anticancer activity (63,64). Some studies report that curcumin has drug interactions. Liu et al.,(29) conducted warfarin 0.2 mg/kg with oral administration of 25 mg/kg curcumin, 50 mg/kg, and 100 mg/kg to rats for 7 days show that curcumin had no effect on pharmacodynamics of warfarin. However administration of 100 mg/kg of curcumin significantly increased $\text{AUC}_{0-\infty}$ and $C_{\text{max}}$. When compared to the control group, 100 mg/kg of curcumin increased 1.6 times higher $\text{AUC}_{0-\infty}$ value and 1.5 times higher of $C_{\text{max}}$, whereas plasma clearance decreased by 57.14% and there is no change in $T_{1/2}$. Interaction of warfarin and curcumin is achieved by inhibit P-glycoprotein and increase warfarin absorption.

In conclusion, the administration of curcumin at a dose of 100 mg/kg affects pharmacokinetics but does not affect the pharmacodynamics of warfarin (29). However, the co-administration of curcumin and warfarin must still be monitored to minimize the side effects.

3.8 Caffeine

Caffeine is widely consumed in the community so that it allows interactions with drugs. Coffee and tea are the main sources of caffeine. Zafar et al (30) showed that administration of 0.5 mg/kg warfarin and caffeine 5 mg/kg to rabbits has no significant effect on the $C_{\text{max}}$, $T_{\text{max}}$, and $Vd$ (Table 1), but there were changes of warfarin $T_{1/2}$ when compared with the control group. This result indicates that multiple doses of caffeine increase $T_{1/2}$ of warfarin. Furthermore, the total clearance of warfarin when it was given together with caffeine was lower than control, caffeine reduced the elimination of warfarin from the body. Also, AUC has a significant increased (Table 1) after the administration of caffeine with warfarin, it means that caffeine inhibits warfarin metabolism. The inhibition is due to blocking CYP1A2 and CYP3A4 (30). In conclusion, caffeine can affect the pharmacokinetic profile of warfarin, so the co-administration of caffeine and warfarin needs to be reconsidered.

3.9 Challenge and Future Perspective

The co-administration of warfarin with herbs needs to be considered because they cause interactions. It is better to consume these herbs 1-2 hours after consuming warfarin to prevent their adverse effects. The effect of the pharmacokinetic interactions is an increase in drug levels in the blood, this can be dangerous, whereas the effects of this pharmacodynamic warfarin interaction are bleeding, bruising, fatigue, gastrointestinal effects, hemorrhage and thrombosis (65). In the future, more extensive research needs to be done to find out interactions with other herbs, in addition it is also necessary to do in depth research to study the mechanism of the interaction.

4. Conclusion

It can be concluded that some herbal medicines have significant interactions with warfarin based on pharmacokinetic and pharmacodynamic parameters. The herbs that affect the pharmacokinetics of warfarin are Danshen gegen, echinacea, *St. John's wort* and caffeine. While herbs those affect the pharmacodynamics of warfarin are policosanol, *Ginkgo biloba*, Cranberry, *St. John's wort*, ginseng, pomegranate peel, guava leaves and curcumin, so the administration of warfarin with those herbs need more concerned.
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