

Appendix

Mechanism of interaction: danshen on warfarin

Pharmacodynamic: Danshen contains coumarin derivatives,⁽³³⁾ and has been found to exhibit antiplatelet effects by inhibiting platelet aggregation using platelet cAMP.⁽³⁴⁾

Pharmacokinetic: *In vitro* studies have found that tanshinones in danshen inhibit CYP1A1, 2C6 and 2C11-mediated warfarin metabolism, and that sodium tanshinone IIA sulfonate replaces warfarin from the binding site on human serum albumin-warfarin complex, increasing free warfarin concentration in blood.^(35,36) However, *in vivo* and *ex vivo* studies have found that danshen components induce CYP3A4 in humans, and CYP1A, 2C and 3A in mice.^(37,38)

Mechanism of interaction: ginkgo on warfarin

Pharmacodynamic: In a crossover study (n = 6), BN52063 in ginkgo was found to inhibit platelet-activating factor-induced platelet aggregation.⁽³⁹⁾ However, another crossover trial (n = 50) found no effect of EGb761 on platelet aggregation or blood coagulation, and no relationship between EGb761 and haemorrhagic complications.⁽⁴⁰⁾

Pharmacokinetic: *In vitro* studies with human microsomes and animal studies found that *Ginkgo biloba* extract and active components (flavonoidic and terpenoidic fractions of EGb761) significantly inhibit CYP1A2, 2E1, 2C9, 3A4, 2C19, which may interfere with metabolism of warfarin.^(41,42) However, other studies have yielded conflicting results. An animal (mice) study concluded that warfarin anticoagulation effects were significantly attenuated by *Ginkgo biloba* extract and bilobalide, which decreased the concentration of R-warfarin by inducing CYP1A1, 1A2, 2B, 2C and 3A.⁽⁴³⁾ In elderly volunteers, ginkgo had no effect on CYP3A4, 2D6, 2E1 and 1A2 when midazolam, debrisoquine, chlorzoxazone and caffeine were used as probes.⁽⁴⁴⁾

Mechanism of interaction: dong quai on warfarin

Pharmacodynamic: Dong quai contains coumarin constituents (ferulic acid, osthole) which have been shown to inhibit platelet aggregation.⁽³³⁾ Animal steady state studies have found that Dong quai significantly increased PT⁽⁴⁵⁾ without any effect on warfarin concentration, suggesting the presence of pharmacodynamics, but not pharmacokinetic interactions.

Mechanism of interaction: safflower on warfarin

Pharmacodynamic: A clinical study of healthy volunteers (n = 30) found that 3 weeks of safflower oil and canola oil diets significantly reduced platelet aggregation.⁽⁴⁶⁾

Mechanism of interaction: peach kernel on warfarin

Pharmacodynamic: Animal studies have found that peach kernel has antiplatelet and anticoagulation effects. Ethanol extract inhibits platelet aggregation, and petroleum ether extract prolongs thrombin time.⁽⁴⁷⁾

Mechanism of interaction: licorice on warfarin

Pharmacokinetic: the supratherapeutic effects of licorice on warfarin can be explained by experimental studies, which showed pharmacokinetic inhibition of CYP3A4, 2B6, 2C9 of glabridin.⁽⁴⁸⁾

Pharmacodynamic: Licorice components, glycyrrhizin and GU-7, have been found to exhibit antiplatelet activity in rabbit and human *in vitro* studies.^(49,50) However, in experimental rat studies, licorice has been found to activate pregnane X receptor *in vitro* and increase warfarin metabolism *in vivo*. If these results are extrapolated, licorice may reduce the antithrombotic effect of warfarin.⁽⁵¹⁾

Mechanism of interaction: Asian ginseng on warfarin

Pharmacokinetic: *In vitro* studies (human) have found that ginseng extract, constituents (kaempferol) and metabolites (compound K, protopanaxadiol, protopanaxatriol) inhibit CYP450 enzymes (CYP3A4, 2C9, 2C19, 2D6), which are involved in the metabolism of warfarin.⁽⁵²⁻⁵⁴⁾ However, a randomised crossover study of healthy volunteers (n = 24) found that *Panax ginseng* had a nonclinically significant effect on the clearance of warfarin.⁽⁵⁵⁾ Also, 28 days of *Panax ginseng* (1,500 mg/day) use in both young (mean age 25 years) and elderly (mean age 67 years) healthy volunteers had no effect on CYP3A4, 2E1 and 1A2 activities. Although CYP2D6 was significantly inhibited by *Panax ginseng* in the elderly, the magnitude of the effect was not clinically significant.^(44,56)

Pharmacodynamic: Antiplatelet and anticoagulant effects have also been described. *In vitro* studies (rabbit, rat, human) found that ginseng and its components (panaxynol, ginsenosides Ro, Rg1, Rg2, lipophilic fraction) inhibit platelet aggregation, possibly by regulating the levels of cGMP and TXA2, as well as inhibit release reaction and thromboxane formation.⁽⁵⁷⁻⁵⁹⁾ A recently published *in vitro* study found that *Panax ginseng* water extract (0.05 mg/mL), Rg1 and Rg2 significantly extended blood clotting time in human plasma as compared to that of the control group.⁽¹⁸⁾ However, a crossover trial of healthy adults (n = 10) found no significant alteration of platelet function after two weeks of ginseng consumption in recommended doses.⁽⁶⁰⁾

Mechanism of interaction: lycium on warfarin

Pharmacokinetic: An *in vitro* study found that lycium weakly inhibits S-warfarin metabolism by CYP2C9, but the dissociation constant (Ki) value of 3.4 mg/mL suggests that other factors other than the CYP450 system may be responsible for the interaction.⁽⁶¹⁾

Mechanism of interaction: ginger on warfarin

Pharmacodynamic: Ginger (5 g dose) has been found in randomised placebo-controlled trials to inhibit platelet aggregation, possibly by inhibiting platelet COX products and thromboxane synthetase, and increase fibrinolytic activity.⁽⁶²⁻⁶⁴⁾ However, an open-label, three-way crossover, randomised study (n = 12) found no evidence of pharmacodynamics or pharmacokinetic interaction with warfarin.⁽¹⁵⁾

Mechanism of interaction: notoginseng on warfarin

Pharmacodynamic: *In vitro* studies (human, rat) found that both raw and steamed *Panax notoginseng* exhibits antiplatelet activity, and significantly inhibited platelet aggregation and plasma coagulation. This was positively translated to prolongation of *in vivo* rat bleeding time at a dosage of 500 mg/kg.^(65,66)