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Review

Concomitant use of prescription medications and dietary supplements in menopausal women: An approach to provider preparedness

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ABSTRACT

Dietary supplements are becoming increasingly popular as therapies for symptom relief among menopause-age women in the United States. However, a large gap exists between research in the concomitant use of prescription medications and dietary supplements and provider preparedness to guide patient decision making. Many menopausal women take prescription medications, over the counter medications, and herbs and dietary supplements for climactic symptoms or other health conditions. With any drug, there is the potential for interactions. Women taking medications with a narrow therapeutic index, such as anticoagulants, anticonvulsants, and drugs for the treatment of chronic diseases, are at particular risk. Patients should be queried regarding their use of dietary supplements when starting or stopping a prescription drug, or if unexpected reactions occur. When counseling patients, one must carefully consider the risks and benefits of each supplement and medication being taken by each individual.

Contents

1. Introduction

Prior surveys report that 50–80% of women use some type of complementary and alternative medicine (CAM) which includes dietary supplements, i.e., nutrients and herbs [1,2]. Insomnia, depression, memory enhancement, chronic gastrointestinal disorders, and pain top the list of medical conditions for which middle-aged women use non-vitamin supplements [3], and they also frequently use dietary supplements to prevent or treat menopause-related symptoms. In a survey of 1296 women aged 45–65, 54% reported using CAM, with soy (25%) and evening primrose oil (18%) being the most popular dietary supplements. Of the 60% of respondents currently taking prescription or over-the-counter pharmaceuticals, 63% reported using CAM products during the past 12 months

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[4].

2. Interactions and polypharmacy

The issue of polypharmacy is amplified in the aging population. Qato et al. [5] found that among older adults in the United States, 29% were taking at least five prescription medications concurrently, 81% used at least one prescription medication, 42% used at least one over-the-counter medication, and 49% were taking a dietary supplement. Additionally, Nahin et al. [6] reported substantial concomitant use of prescription drugs and dietary supplements among 3070 ambulatory individuals aged 75 and older. Almost three-quarters (74%) of the study cohort reported using at least one prescription drug and one dietary supplement, with 33% using three or more prescription drugs and three or more supplements. Although supplements were taken concomitantly with all classes of prescription drugs, the use of supplements was more likely in individuals using nonsteroidal anti-inflammatory drugs, thyroid hormone, and estrogens. It may be that many individuals simply do not see these classes of drugs as medications with which they need to exercise caution. In some cases, patients may self-medicate with non-prescription agents in an attempt to mitigate some of the adverse effects of pharmaceuticals, not knowing that the combination might actually increase the risk.

3. Disclosure to health care professionals

There is an all too common lack of communication between physicians and patients on the use of CAM, which makes monitoring the use of medications difficult [7]. In a study of menopause-aged women, 45% used some form of CAM and 25% used herbal products. Yet, only 45% of CAM users mentioned its use to a medical provider and the odds for CAM use were almost twice as high for women with menopausal symptoms in the past year compared with women with no symptoms [8]. A national survey found more than one third of respondents declared they did not disclose the use of CAM to their doctors because "the doctor would not understand" (20%), "would disapprove of or discourage CAM use" (14%) or "might not continue as their provider" (2%) [9].

4. State of the evidence for medication/dietary supplement interactions

Dietary supplements are not subjected to the rigorous premarketing approval process required of prescription drugs. As a result, we often have incomplete knowledge regarding interactions between dietary supplements and pharmaceuticals, as well as adverse effects associated with herbs and nutrients. More specifically, there is no requirement for systematic evaluation of dietary supplement products for possible interactions with drugs commonly used by menopausal women. Limited pharmacologic data have been published for the large number of herbs available in the marketplace and even fewer about products that contain multiple herbs, which is the norm rather than the exception. As a result, our knowledge of interactions is incomplete and more often than not based on animal studies, case reports, case series, historical contraindications, extrapolation from basic pharmacology research, and repetitious regurgitation of speculative and/or outdated data. Randomized double-blinded clinical trials in the area are rare and the vast majority of published case reports provide unqualified and/or inadequate detail to enable any systematic and substantiated conclusions. The scientific literature covering interactions between pharmaceutical agents and dietary supplements or other complementary and alternative medicines (CAM) are largely understudied and available reference resources underutilized.

In addition to the lack of pharmacokinetic data, there are still concerns regarding the quality and consistency of products, particularly when it comes to herbal preparations. Herbs contain complex mixtures of constituents that can vary extensively depending on growth and harvesting conditions, as well as processing and formulation variables that can influence the quality, safety, and effectiveness of the finished herbal product [10]. Finished products may also be adulterated with pharmaceuticals that can be very hard to detect using traditional laboratory analysis. Fourteen out of twenty herbal medicines or dietary supplements marketed as natural slimming products were found to be adulterated with undeclared pharmaceuticals, including sibutramine, phenolphthalein, and synephrine [11]. A number of randomly purchased Chinese/patent medicines from Chinatown retail stores in New York City were found to contain undeclared pharmaceuticals including promethazine, chlormethiazole, chlorpheniramine, diclofenac, chlordiazepoxide, hydrochlorothiazide, triamterene, diphenhydramine and sildenafil [12]. Similar concerns have been voiced regarding heavy metal contaminants and other quality control issues with Ayurvedic herbal products from India [13]. Whilenot representative of all Asian herbal products on the market, these cases are deeply disturbing, as it is all but impossible for the consumer or clinician to adequately predict an adverse reaction or interaction if the dietary supplement contains contaminants, undeclared ingredients or is adulterated with pharmaceuticals. Here patients are cautioned in their role as self-care consumers and advised to consult with a healthcare provider trained and experienced in botanical medicine, both in regard to personalized prescribing and in selection of high quality products that meet or exceed GMP standards.

4.1. Types of interactions

The pharmacology of interactions varies greatly based upon the individual woman, her physiology, pharmacogenomics, medical history, co-morbidities and co-medications. Additionally, her diet, lifestyle and compliance to prescription and non-prescription medications affect her risk of interactions. In the menopausal and post-menopausal woman, organ function, drug detoxification systems, and variability and complexity in physiologic function combine to enhance the risk of adverse reactions [14,15].

By treating all substances as pharmacological agents on a level playing field, whether prescription, over-the-counter, or dietary supplements, we can benefit from applying the disciplines of pharmacodynamics and pharmacokinetics. *Pharmacokinetic* interactions result from changes in metabolism, excretion, absorption, or protein binding of the drug, resulting in either more pronounced or diminished pharmacologic activity. *Pharmacodynamic* interactions occur when the intrinsic action of one substance augments or antagonizes the activity of another.

5. Herb interactions in specific menopausal patients: a case based approach

5.1. A healthy woman taking estrogen replacement

Caroline is a 49-year-old woman with unbearable hot flashes that interfered with her life and adversely affected her sleep. After a careful, thorough, informed discussion with her clinician, she decided to take hormone therapy (HT). The dose of HT she was taking did not completely alleviate her hot flashes, so added Saint John's wort (*Hypericum perforatum*) to her routine, hoping she will gain additional benefit without having to increase her dose of HT.

Table 1
Dietary supplements, CYP3A4, and hormone therapy.

	Interaction with HT
Black cohosh (*Actaea racemosa* L.; *Cimicifuga racemosa* [L.] Nutt.)	Does not interact with CYP3A4 substrates in humans
Ginseng (*Panax ginseng*)	Does not interact with CYP3A4 substrates in humans
Saint John's wort (*Hypericum perforatum*)	May reduce the level of HT as it induces CYP3A4
Soy (*Glycine max*)	Does not interact with CYP3A4 substrates in humans but did interact in in vitro

Discussion: It is not unusual for women who take HT to also use dietary supplements. In an online survey by Ma et al. 37% of 781 US women aged 40–60 years reported using HT. Herbal products (31%) and soy supplements (13%) were used among symptomatic women, of whom 41% and 67% were current HT users. Forty-four percent of herb users considered these products helpful with symptom relief. Women generally felt poorly informed about the proper dose and usage of herbal products and 58% expressed at least some concern about using these products; proven safety was the most important factor women considered when using dietary supplements [16].

According to in vitro and in vivo studies, estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4), thus inhibitors or inducers of CYP3A4 may affect estrogen metabolism. St. John's wort induces CYP3A4 and interacts with p-glycoprotein, making it theoretically possible that it might increase the metabolism of estrogen [17,18]. To date, the only human studies evaluating the interaction between St. John's wort and estrogen were conducted using oral contraceptives, and a reduction in serum estradiol was observed [19–21]. The results of a phase II trial sponsored by the National Cancer Institute evaluating the effectiveness of St. John's wort for relieving hot flashes in postmenopausal women with non-metastatic breast cancer will be published soon. If the results of the trial are positive, more women may use St. John's Wort for symptomatic relief of hot flashes. Clinicians should be alert to other medications metabolized by CYP3A4 that might interact with St. John's wort. Table 1 outlines the herbs commonly used in menopause and possible interactions with HT [22–24].

5.2. A woman with osteoporosis

Francis is a 63-year-old Caucasian woman with a history of hypertension, mild hyperlipidemia, and osteoporosis, who is here for her annual exam. She is doing well overall but reports that she has noticed some loss of taste and smell over the past 2–3 months. Her blood pressure has been stable on captopril for the past 12 months and she has been trying to treat her lipid abnormalities with diet and exercise. She is currently taking alendronate 70 mg weekly, and applying topical estrogen cream, twice weekly. She is not taking any calcium or vitamin D supplements as she thought that the bisphosphonate and estrogen cream were all she needed to support bone integrity.

Discussion: This woman's case is representative of the polypharmacy often seen in older patients. It is possible that the loss of taste and smell she is experiencing is due to her use of captopril. The ACE inhibitors, ARBs and to some degree thiazide diuretics, are associated with zinc deficiency secondary due to increased urinary loss [25]. Zinc deficiency can lead to diminished taste and smell, as well as slowing wound healing, alopecia and decreased immune function. A multivitamin that provides the daily allowance for zinc and copper (required when taking zinc) would be a good idea.

Francis has been diagnosed with osteoporosis and is on weekly alendronate. All currently approved bone-active pharmacological agents have been studied in conjunction with supplemental calcium. The clinician should estimate her total daily dietary intake for calcium with a goal of 1500 mg per day. Calcium supplements should be used to make up any difference between her dietary intake and calcium goal. Calcium citrate would be preferable to carbonate given her age and likelihood of low gastric acid production. Co-administration of magnesium may be helpful as it can counter the highly constipating effects of calcium, may have a beneficial effect on hypertension and also helps in bone maintenance and integrity [26,27]. Advising the patient to separate the intake of calcium from other medications is highly advisable, as minerals tend to bind with many substances, reducing assimilation.

All women with osteoporosis should have their 25(OH)D level checked at least annually and vitamin D3 administered at doses sufficient to achieve a serum level of 40 ng/ml (100 nmol/l) [28]. Vitamin D3 (cholecalciferol) should be taken with food to enhance absorption [29].

5.3. A woman with breast cancer on tamoxifen

Jenny is a 48-year-old Hispanic woman with hormone receptor positive breast cancer who has completed adjuvant chemotherapy and radiation. She is now taking daily tamoxifen. Jenny's hot flashes bother her all day long and are worse at night. She has been highly irritable and is now taking black cohosh (40 mg per day standardized extract) and valerian (300 mg standardized extract before bed) to help both her hot flashes and sleep. She is taking ibuprofen 800 mg TID and tramadol PRN for the dull ache in her left breast that resulted from radiation therapy. Her friend recommended that she take fish oil (1400 mg EPA plus 600 mg DHA) to reduce inflammation and possibly reduce her need for pain medication.

Discussion: Many women with breast cancer use CAM and dietary supplements to help relieve the symptoms and side effects associated with treatment [30]. Although some women find improvement in their symptoms, there may also be some associated risk. For example, if a product acts as an estrogen or progesterone agonist, this may be detrimental for a woman with a hormonally sensitive cancer (e.g., estrogen-responsive breast cancer, endometrial cancer). There are also concerns that certain dietary supplements might reduce the effectiveness of chemotherapy, radiation, tamoxifen or aromatase inhibitor treatments.

Clinical trials and a systematic review of breast cancer clinical and preclinical studies to assess the effect of black cohosh on breast cancer have been published. There were no reported interactions between tamoxifen and black cohosh in clinical trials [31–33], however, there is some human pharmacokinetic data indicating that the herb mildly inhibits CYP2D6, the enzyme system responsible for the metabolism of tamoxifen, though it is unclear if this interaction is clinically relevant [22].

5.4. A woman taking warfarin

Cindy is a 55-year-old woman with vaginal dryness, hot flashes and frequent urinary tract infections (UTI). She recently started taking daily cranberry capsules to prevent UTI and vitamin E capsules (800 IU/d d-alpha tocopherol) for her menopausal symptoms. Cindy has been on warfarin for atrial fibrillation for the past two years.

Discussion: Pharmacogenomic variability in response to warfarin is significant and it is widely known that many foods and medications can potentially affect the drug's effectiveness [34]. Therefore, it is critical to understand how dietary supplements affect the hematological system to avoid risk of bleeding or clotting

Table 2
Dietary supplements, warfarin, and clinical recommendations.

Dietary supplement	Strength of documentation	Clinical recommendation
Ginkgo (*Ginkgo biloba*)	Possible, though controlled clinical studies show no effect of ginkgo on the kinetics or dynamics of warfarin	Some experts recommend caution, given the major severity of the effect, although available research does not support this conclusion.
Cranberry (juice) (*Vaccinium macrocarpon*)	Suspected based on 7 reports of increased INR, though a recent clinical study showed no interactions	Low probability of clinically significant interaction but prudence warrants regular monitoring of INR and substance intake.
Fish oil	Case reports of elevated INR though a clinical study showed no effect of fish oil on anticoagulation status	Check independent increased bleeding with fish oil.
Ginseng American ginseng (*Panax quinquefolius*) (*Panax ginseng*)	Possibly based on conflicting research findings. American Ginseng reduces blood concentrations warfarin Coadministration of warfarin with Asian (*Panax*) ginseng did not affect the pharmacokinetics or pharmacodynamics of warfarin	Avoid if possible given the narrow therapeutic index of warfarin. Close monitoring of INR advisable if ginseng deemed appropriate, at least during introduction or with dose change.
Vitamin E (>400 IU/day)	Suspected based on a single patient (with re-challenge), resulting in an increase in INR One clinical trial that showed no interaction	Clinically significant interaction improbable. Monitor warfarin response when vitamin E is used in combination, especially during introduction or with dose change.
St. John's wort (*Hypericum perforatum*)	Suspected based on decreases in INR in case reports and in a study in 12 healthy volunteers	Monitor warfarin response when St. John's wort is started or stopped or when a new bottle is started or dose changed.
Garlic (*Allium sativum*)	Unlikely, based on a recent clinical study that found garlic is relatively safe and poses little or no serious hemorrhagic risk for closely monitored patients on warfarin oral anticoagulation therapy	Due to garlic's antiplatelet effects monitoring is prudent.
	One review found no qualified case reports of interactions with garlic and warfarin	Risk is over anticoagulation.

[35]. The degree of bleeding risk associated with vitamin E remains controversial and caution is warranted in women taking warfarin. Concomitant use of vitamin E with antiplatelet agents like aspirin might increase the risk of bleeding by inhibiting platelet aggregation [36] However, a clinical trial with warfarin and vitamin E showed no increased risk of bleeding [37].

Cranberry juice, though implicated in case reports, has not been shown to affect coagulation in a controlled study [38]. Therefore there is a low probability of added risk to Cindy using cranberry while taking warfarin.

Other herbs that women might use during the menopausal transition have been investigated for possible interaction with antiplatelet and anti-coagulant medications. Garlic (*Allium sativum*) has intrinsic antiplatelet activity, however, a clinical trial showed that garlic is safe and poses minimal to no risk of clinically significant hemorrhagic adverse events in closely monitored warfarinized patients [39]. Ginkgo (*Ginkgo biloba*) does not interact with warfarin or aspirin directly, but has demonstrated antiplatelet activity [40]. Asian ginseng (*Panax ginseng)* has been evaluated in one methodologically weak study and does not seem to interact with warfarin [41]. However, American ginseng (*Panax quinquefolius*) decreases warfarin serum levels, resulting in decreased anticoagulant activity [39,42]. Eleuthero (*Eleutherococcus senticosus*), also referred to as "Siberian ginseng," has not been adequately studied, though it contains a constituent that inhibits platelet aggregation. Table 2 is a summary of important interactions between warfarin and dietary supplements [38,41,43–48].

Given the narrow therapeutic index of warfarin and the serious consequences associated with small changes in blood levels, patients taking dietary supplements should be carefully monitored. Anticoagulation status should be checked whenever patients start or stop taking a supplement. Abrupt changes in supplement use or dietary constituents/composition are generally to be avoided in warfarinized patients with regular monitoring and titration being the operative themes of prudent management.

6. Conclusion

In conclusion, many patients using vitamins, minerals, other nutrients, and herbs, define these familiar substances as "natural or safer" than prescription medications. It is important to ask all patients about the dietary supplement to avoid unnecessary interactions or adverse events. Treat all substances as pharmacological agents on a level playing field, whether prescription, over-the-counter, or dietary supplements.

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Contributors

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Competing interests

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References

[1] Park K, Harnack L, Jacobs Jr DR. Trends in dietary supplement use in a cohort of postmenopausal women from Iowa. Am J Epidemiol 2009;1169(April (7)):887–92.
[2] Gold EB, Bair Y, Zhang G, et al. Cross-sectional analysis of specific complementary and alternative medicine (CAM) use by racial/ethnic group and menopausal status: the Study of Women's Health Across the Nation (SWAN). Menopause 2007;14(July–August (4)):612–23.
[3] Gardiner P, Graham RE, Legedza A, Eisenberg DM, Phillips RS. Factors associated with dietary supplement use among prescription medication users. Arch Intern Med 2006;166:1968–74. PMC journal- in process.
[4] Van der Sluijs CP, Bensoussan A, Liyanage L, Shah S. Women's health during mid-life survey: the use of complementary and alternative medicine by symptomatic women transitioning through menopause in Sydney. Menopause 2007;14(May–June (3 Pt 1)):397–403.
[5] Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA 2008;300(December (24)):2867–78.
[6] Nahin RL, Pecha M, Welmerink DB, et al. Concomitant use of prescription drugs and dietary supplements in ambulatory elderly people. J Am Geriatr Soc 2009;57(July (7)):1197–205.
[7] Cardini F, Lesi G, Lombardo F, van der Sluijs C. The use of complementary and alternative medicine by women experiencing menopausal symptoms in Bologna. BMC Womens Health 2010;10:7.
[8] Brett KM, Keenan NL. Complementary and alternative medicine use among midlife women for reasons including menopause in the United States 2002. Menopause 2007;14(March–April (2)):300–7.
[9] Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States Prevalence, costs, and patterns of use. N Engl J Med 1993;328(January (4)):246–52.
[10] Low Dog T. Assessing safety of herbal products for menopausal complaints: an international perspective. Maturitas 2010;66:355–62.
[11] Vaysse J, Balayssac S, Gilard V, Desoubdzanne D, Malet-Martino M, Martino R. Analysis of adulterated herbal medicines and dietary supplements marketed for weight loss by DOSY ^{1}H NMR. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2010;27(July (7)):903–16.
[12] Miller GM, Stripp R. A study of western pharmaceuticals contained within samples of Chinese herbal/patent medicines collected from New York City's Chinatown. Leg Med (Tokyo) 2007;9(September (5)):258–64.
[13] Saper RB, Kales SN, Paquin J, et al. Heavy metal content of ayurvedic herbal medicine products. JAMA 2004;292(December (23)):2868–73.
[14] Williams C. Using medications appropriately in older adults. Am Fam Physician 2002;66(10):1917–24.
[15] Anantharaju A, Feller A, Chedid A. Aging liver: a review. Gerontology 2002;48(November–December (6)):343–53.
[16] Ma J, Drieling R, Stafford RS. US women desire greater professional guidance on hormone and alternative therapies for menopause symptom management. Menopause 2006;13(May–June (3)):506–16.
[17] Gurley BJ, Gardner SF, Hubbard MA, et al. Cytochrome P450 phenotypic ratios for predicting herb-drug interactions in humans. Clin Pharmacol Ther 2002;72(September (3)):276–87.
[18] Hennessy M, Kelleher D, Spiers JP, et al. St Johns wort increases expression of P-glycoprotein: implications for drug interactions. Br J Clin Pharmacol 2002;53(January (1)):75–82.
[19] Pfrunder A, Schiesser M, Gerber S, Haschke M, Bitzer J, Drewe J. Interaction of St John's wort with low-dose oral contraceptive therapy: a randomized controlled trial. Br J Clin Pharmacol 2003;56(December (6)):683–90.
[20] Will-Shahab L, Bauer S, Kunter U, Roots I, Brattstrom A. St John's wort extract (Ze 117) does not alter the pharmacokinetics of a low-dose oral contraceptive. Eur J Clin Pharmacol 2009;65(March (3)):287–94.
[21] Fogle RH, Murphy PA, Westhoff CL, Stanczyk FZ. Does St. John's wort interfere with the antiandrogenic effect of oral contraceptive pills? Contraception 2006;74(September (3)):245–8.
[22] Gurley BJ, Gardner SF, Hubbard MA, et al. In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. Clin Pharmacol Ther 2005;77(May (5)):415–26.
[23] Wang G, Xiao CQ, Li Z, et al. Effect of soy extract administration on losartan pharmacokinetics in healthy female volunteers. Ann Pharmacother 2009;43(June (6)):1045–9.
[24] Li Y, Ross-Viola JS, Shay NF, Moore DD, Ricketts ML. Human CYP3A4 murine Cyp3A11 are regulated by equol and genistein via the pregnane X receptor in a species-specific manner. J Nutr 2009;139(May (5)):898–904.
[25] Dunn SP, Bleske B, Dorsch M, Macaulay T, Van Tassell B, Vardeny O. Nutrition and heart failure: impact of drug therapies and management strategies. Nutr Clin Pract 2009;24(February–March (1)):60–75.
[26] Stendig-Lindberg G, Tepper R, Leichter I. Trabecular bone density in a two year controlled trial of peroral magnesium in osteoporosis. Magnes Res 1993;6:155–63.
[27] Tucker KL. Osteoporosis prevention and nutrition. Curr Osteoporos Rep 2009;7(December (4)):111–7.
[28] Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005;293(May (18)):2257–64.
[29] Heaney RP, Weaver CM. Calcium vitamin D. Endocrinol Metab Clin North Am 2003;32(March (1)):181–94.
[30] Eschiti VS. Lesson from comparison of CAM use by women with female-specific cancers to others: it's time to focus on interaction risks with CAM therapies. Integr Cancer Ther 2007;6(December (4)):313–44.
[31] Walji R, Boon H, Guns E, Oneschuk D, Younus J. Black cohosh (Cimicifuga racemosa [L.] Nutt.): safety and efficacy for cancer patients. Supportive Care Cancer 2007;15(August (8)):913–21.
[32] Jacobson JS, Troxel AB, Evans J, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. J Clin Oncol 2001;19(May (10)):2739–45.
[33] Rebbeck TR, Troxel AB, Norman S, et al. A retrospective case-control study of the use of hormone-related supplements and association with breast cancer. Int J Cancer 2007;120(April (7)):1523–8.
[34] Kamali F, Wynne H. Pharmacogenetics of warfarin. Annu Rev Med 2010;61:63–75.
[35] Grady D. Postmenopausal hormone replacement therapy increases risk for venous thromboembolism disease: the heart and estrogen/progestin replacement study. Ann Intern Med 2000;132:689–96.
[36] Celestini A, Pulcinelli FM, Pignatelli P, et al. Vitamin E potentiates the antiplatelet activity of aspirin in collagen-stimulated platelets. Haematologica 2002;87(April (4)):420–6.
[37] Kim JM, White RH. Effect of vitamin E on the anticoagulant response to warfarin. Am J Cardiol 1996;77(March (7)):545–6.
[38] Greenblatt DJ, von Moltke LL, Perloff ES, Luo Y, Harmatz JS, Zinny MA. Interaction of flurbiprofen with cranberry juice, grape juice, tea, and fluconazole: in vitro and clinical studies. Clin Pharmacol Ther 2006;79(January (1)):125–33.
[39] Bebbington A, Kulkarni R, Roberts P. Ginkgo biloba: persistent bleeding after total hip arthroplasty caused by herbal self-medication. J Arthroplasty 2005;20(January (1)):125–6.
[40] Jiang X, Williams KM, Liauw WS, et al. Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 2005;59(April (4)):425–32.
[41] Jiang X, Williams KM, Liauw WS, et al. Effect of St John's wort and ginseng on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. Br J Clin Pharmacol 2004;57(May (5)):592–9.
[42] Yuan CS, Wei G, Dey L, et al. Brief communication: American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled trial. Ann Intern Med 2004;141(July (1)):23–7.
[43] Bender NK, Kraynak MA, Chiquette E, Linn WD, Clark GM, Bussey HI. Effects of marine fish oils on the anticoagulation status of patients receiving chronic warfarin therapy. J Thromb Thrombolysis 1998;5(July (3)):257–61.
[44] Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. Am J Cardiol 1996;77(January (1)):31–6.
[45] Buckley MS, Goff AD, Knapp WE. Fish oil interaction with warfarin. Ann Pharmacother 2004;38(January (1)):50–2.
[46] Corrigan Jr JJ, Marcus FI. Coagulopathy associated with vitamin E ingestion. JAMA 1974;230(December (9)):1300–1.
[47] Macan H, Uykimpang R, Alconcel M, et al. Aged garlic extract may be safe for patients on warfarin therapy. J Nutr 2006;136(March (3 Suppl.)):793S–5S.
[48] Vaes LP, Chyka PA. Interactions of warfarin with garlic, ginger, ginkgo, or ginseng: nature of the evidence. Ann Pharmacother 2000;34(December (12)):1478–82.