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Artículo de Revisión / Review Article

Warfarin drug interaction with vitamin K and other foodstuffs

Interacción de la droga warfarina con la vitamina K y otros productos alimenticios

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ABSTRACT

Vitamin K is found in higher concentrations in dark green plant and in vegetable oils. The adequate intake of vitamin K is 90 and 120μg/day for adult elderly men and women, respectively. The main function of vitamin K is to act as an enzymatic cofactor for hepatic prothrombin synthesis, blood coagulation factors, and anticoagulant proteins. Prominent among the many available anticoagulants is warfarin, an antagonist of vitamin K, which exerts its anticoagulant effects by inhibiting the synthesis of vitamin K_1 and vitamin KH_2. From the beginning of the therapy it is necessary that the patients carry out the monitoring through the prothrombin time and the international normalized ratio. However, it is known that very low intake and/or fluctuations in vitamin K intake are as harmful as high consumption. In addition, other foods can interact with warfarin, despite their content of vitamin K. The aim of this study was to gather information on the drug interaction of warfarin with vitamin K and with dietary supplements and other foods.

Key words: Drug-food interaction; International Normalized Ratio; Phylloquinone; Sources; Warfarin.

RESUMEN

La vitamina K se encuentra en concentraciones más altas en plantas de color verde oscuro y en aceites vegetales. La ingesta adecuada de vitamina K es de 90 y 120 μg/día para hombres y mujeres adultos mayores, respectivamente. La función principal de la vitamina K es actuar como un cofactor enzimático para la síntesis de protrombina hepática, factores de coagulación de la sangre y proteínas anticoagulantes. Entre los muchos anticoagulantes disponibles destaca la warfarina, un antagonista de la vitamina K, que ejerce sus efectos anticoagulantes al inhibir la síntesis de la vitamina K_1 y la vitamina KH_2. Desde el inicio de la terapia, es necesario que los pacientes realicen el monitoreo a través del tiempo de protrombina y la proporción normalizada internacional. Sin embargo, se sabe que una ingesta muy baja y/o fluctuaciones en la ingesta de vitamina K son tan dañinas como un consumo alto. Además, otros alimentos pueden interactuar con la warfarina, a pesar de su contenido de vitamina K. El objetivo de este estudio fue recopilar información sobre la interacción de los medicamentos de la warfarina con la vitamina K y con los suplementos dietéticos y otros alimentos.

Palabras clave: Filoquinona; Fuentes; Índice Internacional Normalizado; Interacción fármaco-alimento; Warfarina.

INTRODUCTION

Vitamins are essential micronutrients found in small amounts in food and are indispensable to the human organism[1]. The micro-quantities required vary according to the age, sex, physiological state, and physical activity of the individual, with an increased demand during the growth phase, gestation, lactation, intense stress conditions, and the occurrence of certain diseases[2].

Commonly, vitamins are classified as liposoluble and water soluble according to their physiological and physicochemical properties in common[1]. Among the available fat-soluble vitamins is vitamin K, which can be found in three forms: K_1 (phylloquinone), K_2 (menaquinones), and K_3 (menadione)[3].

Vitamin K is present in large quantities in some foods of plant origin, some vegetable oils, and some animal foods[2,4]. Its ingestion is directly related to the synthesis of proteins that participate in blood clotting and bone metabolism[5]. Therefore, irregular consumption of vitamin K may influence the effect of anticoagulants such as warfarin[4,6].

Warfarin is the most widely used anticoagulant in the world and is prescribed to treat and prevent thrombotic disorders, such as atrial fibrillation and deep venous thrombosis, because it is a vitamin K antagonist[7,8].

In this context, the aim of the study was to gather information through literature searches on the drug interactions of warfarin with vitamin K, with emphasis on the food sources and their concentrations in relation to an individual's usual daily consumption, as well as on other interactions with dietary supplements and other foods.

Vitamin K

Vitamin K (2-methyl-3-ethyl-1,4-naphthoquinone) was described in 1929 by Henrik Dam as an antihemorrhagic factor. The name vitamin "K" derives from the first letter of the Danish word "Koagulation," classified as liposoluble[3,9].

Vitamin K can be found in two forms: phylloquinones in photosynthetic plants and vegetable oils, representing the predominant sources of the vitamin; and menaquinones synthesized by bacteria present in the intestinal flora with MK-n coding (where n represents the number of isoprenoid residues in the lipophilic side chain), ranging from MK-4 to MK-13. Menaquinone MK-4 is the only one that is not of bacterial origin, is formed by the rebalancing of menadione present in animal feed or products of conversion of dietetic phylloquinone; and, menadione being a synthetic compound that can be converted into K_2 in the intestine, used as a supplement in animal feed[3,9,10,11].

The required amount of intake for each individual varies according to age, sex, physiological state, and physical activity, and the nutritional requirement may vary according to the periods of growth, lactation, gestation, and illness[2,12]. The recommended dose is 1 µg/kg per day and US guidelines recommend an adequate intake (AI) of 90 and 120 µg/day for adult and elderly men and women, respectively, while the upper tolerable level (UL) has not been established[13]. A study by Booth et al.[14] estimated the intake of vitamin K in adults aged < 45 years as approximately 60-110 µg/day and in adults > 55 years ranging from 80-210 µg/day.

The bioavailability of vitamin K includes cell uptake and conversion to its active form, and depends on the lipid fraction[12,15]. As phylloquinone is associated with photosynthetic tissues, plants contain the highest levels. Fruit and vegetable bark appears to contain higher vitamin concentrations than pulp[3,15].

Vitamin K concentrations vary from 1 µg/100 ml to 400-700 µg/100g in food, with dark green vegetables having the highest levels, contributing 40-50% of the total intake[2]. Other sources of vitamin K are vegetable oils, whose content can range from 0.5-200 µg/100 g. Foods which use in their formulation and preparation some vegetable oils may contain significant concentrations of vitamin K by converting K_1 to 2,3-dihydrofiloquinone (dK) during the hydrogenation process, so it is possible that ultraprocessed foods such as potato chips and fast foods for example, have high levels of vitamin K. Foods such as fruits, some vegetables, foods of animal origin contain lower concentrations of vitamin K (Tables 1, 2)[3,9,10,14,16,17].

However, some factors may affect vitamin K1 concentrations in foods, such as environmental, crop, and geographical factors, and incidence of fluorescent and natural light. However, cooking, freezing, dehydration, and treatment with irradiation do not reduce the concentration of vitamin K[3,15].

In Brazil, there are still no tables with phylloquinone levels in food, so it is necessary to use data from international literature, such as the United States Department of Agriculture (USDA). However, a recent study quantified vitamin K content in vegetables consumed in the city of São Paulo, Brazil[18]; studies such as these are relevant since they may contribute to the evaluation of vitamin K in foods of national origin. In this sense, some differences can be observed in the vitamin K content of some vegetables between the two data sources. For better understanding, information on the vitamin K content per portion of habitual consumption is needed (Tables 1, 2).

Metabolism of vitamin K

Vitamin K from the diet is absorbed in the small intestine and incorporated into the chylomicrons, being transported by the lymphatic pathways, absorbed in the presence of bile salts and pancreatic juice, and taken to the liver[3,9].

Its main function and enzymatic coagulant factor of the enzyme hepatic carboxylase Y-glutamylcarboxylase (GGCX) is required for the hepatic synthesis of prothrombin, blood coagulation factors (II, VII, IX, and X), and regulatory anticoagulant proteins S, C, and Z[9,21] by means of reduction of vitamin K_1-KH_2-hydroquinone by the enzyme vitamin K reductase responsible for the carboxylation reaction of glutamic acid (GLU) acid to form γ-carboxyglutamic acid (GLA). The reduced form of vitamin KH_2 is converted to 2,3-vitamin K by the microsomal enzyme epoxy reductase (VKOR). This metabolite is converted back into vitamin K_1 by the action of VKOR, and vitamin K reductive quinone looks for new carboxylation reactions (Figure 1). Excretion occurs through the kidneys (20%) and feces (40-50%) via bile salts[3,11,22].

Anticoagulant - Warfarin

Oral anticoagulants are one of the classes of drugs most commonly prescribed in pharmacopeia[23]. Among so many oral anticoagulants we have warfarin, which since 1941 has been the basis of oral anticoagulation, being the most used

Table 1. Vitamin K content in portions commonly consumed of vegetables (Source: USDA - United States Department of Agriculture[19]; Faria et al.[18].

High Vit. Foods K (50µg > 100µg)	USDA µg/100g	Faria et al. µg/100g	Portion (g)	Home Measures	Vit. K (µg) portion (USDA)	Vit. K (µg) portion (Faria et al.)
Chard, raw	830	152	14.4	1/2 cup of tea	120	22
Chard, cooked	327.3	122	70	1/2 cup of tea	229	85
Watercress, raw	250	301	20	1/2 cup of tea	50	60
Kale, raw	817	-	27	1/2 cup of tea	221	-
Cooked cauliflower	406.6	-	42	1/2 cup of tea	171	-
Spinach, raw	482.9	375	12	1/2 cup of tea	58	45
Spinach, cooked	493.6	262	72	1/2 cup of tea	355	189
Mustard, raw	257.5	-	22.4	1/2 cup of tea	58	-
Mustard, cooked	592.7	-	56	1/2 cup of tea	332	-
Salsinha	1640	491	4	1 table spoon full	66	20
Foods with Low Vit. K (<50µg)	**USDA µg/100g**	**Faria et al. µg/100g**	**Portion (g)**	**Home Measures**	**Vit. K (µg) portion (USDA)**	**Vit. K (µg) portion (Faria et al.)**
Smooth lettuce	102.3	-	30	4 medium leaves	31	-
Curly lettuce	24.1	-	32	4 medium leaves	8	-
American lettuce	126.3	-	14	1/2 cup of tea	18	-
Broccoli, raw	101.6	279	36	1/2 cup of tea	37	100
Broccoli, cooked	141.1	267	31	1/2 cup of tea	44	83
Chive	207	160	6	1 table spoon full	12	10
Cauliflower, raw	15.5	37	26	1/2 cup of tea	4	10
Cauliflower, cooked	13.8	56	24.8	1/2 cup of tea	3	14
Cabbage, raw	76	328	36	1/2 cup chopped tea	27	118
Cabbage, cooked	108.7	197	30	1/2 cup chopped tea	33	59
Arugula, raw	108.6	289	12	6 sheets	13	35

worldwide, with annual prescriptions equivalent to 0.5-1.5% of the population, despite all its pharmacological challenges, monitoring, and food interactions[4,7,24]. Warfarin is usually prescribed to treat and prevent thrombotic disorders, such as atrial fibrillation and deep venous thrombosis[8].

Warfarin derived from 4-hydroxycoumarin bears a strong resemblance to vitamin K, and is formed by a racemic mixture of the enantiomers S-warfarin (S) and R-warfarin (R) (Figure 2)[7,24,25,26].

The enantiomers of warfarin are metabolized in the liver by different routes, and (S) is metabolized and transformed into inactive metabolites mainly by the enzyme CYP2C, while (R) is metabolized and transformed by CYP1A1/ CYP1A2/ CYP3A4/ CYP2C19, excreted in feces and urine[21,24,26].

Warfarin exerts its anticoagulant effects by inhibiting synthesis of GLA residues by blocking the reduction of oxidized vitamin K in the hepatic carboxylation cycle[3,23,24].

In other words, warfarin inhibits the VKOR enzyme of vitamin K, which prevents its cyclic interconversion, preventing the carboxylation of the GLA residues from the coagulation factors (II, VII, IX, and X), as well as the proteins C, S, and Z (Figure 1)[21,27].

Table 2. Vitamin K content in commonly consumed portions of oils and other foods.

Oil and fat	USDA µg/100g	Portion (g)	Home Measures	Vit. K (µg) portion
Soy oil	183.9	14	1 table spoon	25.7
Cotton oil	24.7	14	1 table spoon	3.5
Canola oil	71.3	14	1 table spoon	10.0
Sunflower oil	5.4	14	1 table spoon	0.8
Coconut oil	0.5	14	1 table spoon	0.1
Corn oil	1.9	14	1 table spoon	0.3
Olive oil	60.2	14	1 table spoon	8.4
Butter with salt	7	10	2 knife tips	0.7
Margarine*	102	10	2 knife tips	10.2
Other Types of Food	**USDA µg/100g**	**Portion (g)**	**Home Measures**	**Vit. K (µg) portion**
Boiled egg	0.3	50	1 large unit	0.2
Potato chips, natural, with salt	22.1	57	1 small package	12.6
Kiwi	40.3	69	1 unit	27.8
Chicken liver, raw	0.0	44	1 liver	0.0
Ox liver, fried	3.9	100	1 steak	3.9
Ox liver, raw	3.1	100	1 steak	3.1
Fermented soybeans (Natto)	23.1	140	1 cup of tea	32.3
Avocado	21	50.25	1/4 avocado	10.6

Source: USDA - United States Department of Agriculture[19]; *Peterson et al.[20].

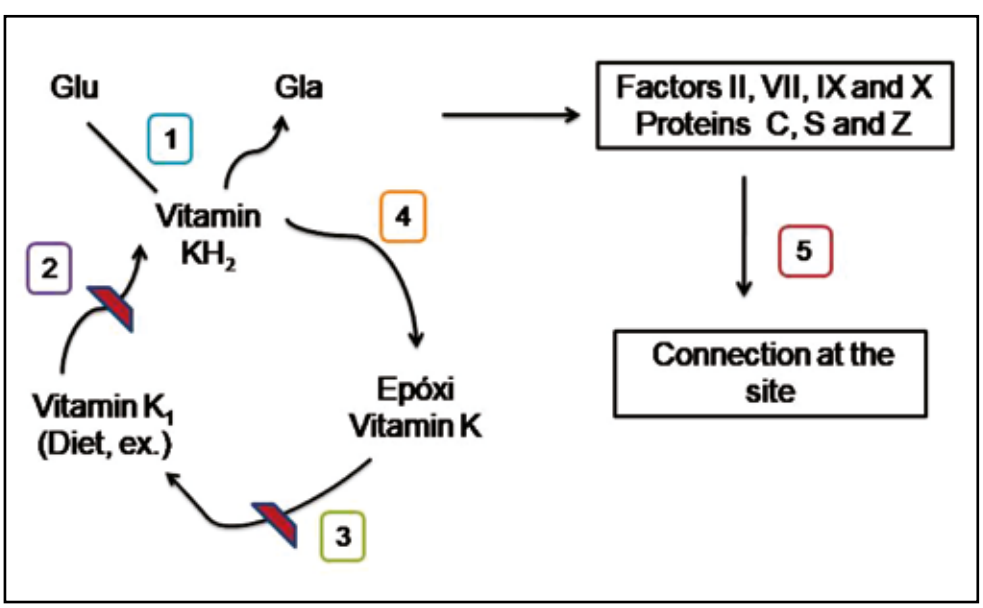

Figure 1. Cycle of Vitamin K. 1) γ-glutamylcarboxylase enzyme (GGCX); 2) vitamin K reductase; 3) microsomal epoxy reductase enzyme (VKOR) and quinone reductases of vitamin K; 4) carboxylation dependent on vitamin K and calcium dependent; 5) Calcium-dependent conformational change. The bars represent the inhibition action of warfarin.
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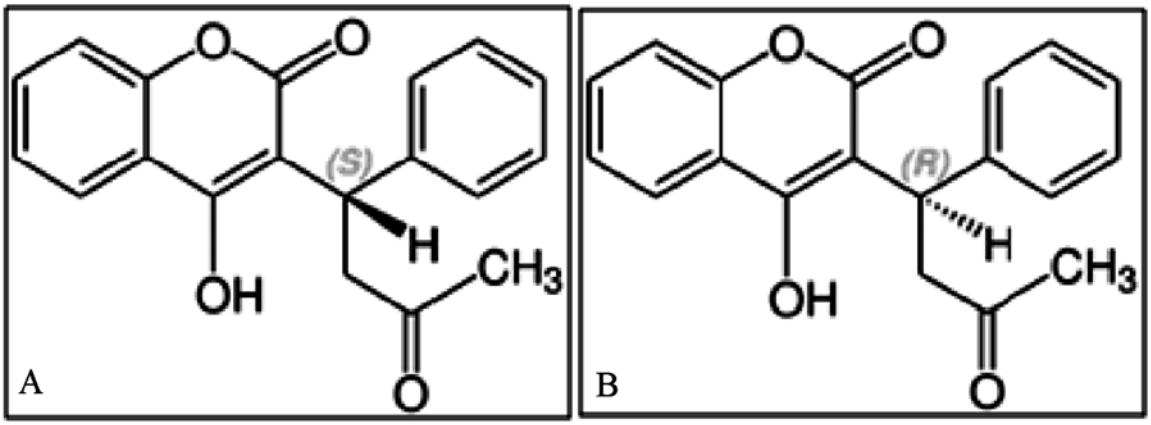

Figure 2. Molecular structure of the enantiomers S-warfarin (a) and R-warfarin (b). Use the original colors of the figure or all black.

Thus, the time between initiation of warfarin administration and onset of action may be explained by the factor clearance rate, so intravascular clots may continue to appear during the first three days of therapy. Action of warfarin after administration remains for 2-5 days[26,27].

Monitoring anticoagulant therapy

From the beginning of warfarin therapy, patients must be monitored through PT and the International Normalized Ratio (INR)[27,28]. This need for monitoring is justified for several reasons, such as narrow therapeutic margin, high drug and food interactions, and the great variability of therapeutic response among individuals[24].

These tests measure the time of clot formation from the activation of factor VII to the formation of the fibrin clot[28]. The PT values are converted to INR by the following equation[29]:

$$INR = (PT_{real} / PT_{ref})^{ISI}$$

in which:
PT_{real}= Measured Prothrombin Time
PT_{ref}= Reference Prothrombin Time
ISI= International Sensitivity Index

The target interval of the INR varies between countries and indications, the most common being 2.0-3.0[24]. Monitoring should be performed every two days until therapeutic INR is achieved, and weekly until stabilized, and then monthly[28]. When the INR is below the therapeutic level, the risk of thrombotic events is higher, since with very high INR hemorrhagic complications increase[30].

Interactions drug / nutrient / food

The potential association between vitamin K intake and coagulation instability has been explored previously in case reports and small retrospective studies[6]. Clinical studies evaluating the effects of vitamin K intake on coagulation parameters in patients using anticoagulants demonstrate that vitamin K intake is directly related to INR[30,31].

According to Park et al.[32], a high rate of vitamin K intake may be an inhibitory factor for patients taking warfarin; in contrast, low vitamin K intake is a risk factor for therapy and for instability of the anticoagulant effect. Khan et al.[25] evaluated the relationship between vitamin K intake and the anticoagulant response to warfarin within a group of subjects over four weeks, and found that for each increase of 100 µg/day in vitamin K intake on average 4 days, the INR would be reduced by 0.2, concluding that the daily intake of vitamin K could be the appropriate strategy to achieve coagulation stability.

Few studies have evaluated the long-term effects of vitamin K intake on the anticoagulant action of warfarin. Kim et al.[33] evaluated the mean intake of vitamin K in patients taking warfarin for more than one year, and its relationship with the stability of the anticoagulant effect. They found that the group that had the highest consumption of vitamin K (> 195.7 µg/day) had a lower INR alteration than the low-intake group (< 126.5 µg/day), concluding that the long-term anticoagulant effect of warfarin is more stable in patients who ingest a greater amount of vitamin K.

Interaction between drug and nutrients is a constant in the evolution of hospitalized patients[34]. However, few studies in the literature show interaction of warfarin with nutrients received in the diet during the period of hospitalization[22,35,36].

Dickerson et al.[35] reported a retrospective case series study evaluating 6 adults who received an enteral diet for 10 consecutive days in warfarin use in which one group received a 3 day diet before and after administration of warfarin, while another group received for 3 days the diet and the medication at the same time. They observed that there was a reduction in the INR response (0.9) in

patients who received warfarin along with the diet. It was concluded that enteral nutrition should be suspended for 1 hour before and after administration of the drug to avoid resistance to warfarin associated with enteral nutrition.

In another study, Dickerson[37] suggests possible causes for reducing the effectiveness of warfarin when ingested along with the enteral diet. He suggests that warfarin resistance may be related to interactions between the drug and enteral formulation and its unavailability for early intestinal absorption, similar to observations already made with other drugs such as phenytoin and fluoroquinolones. Another possible cause of warfarin resistance could be infusion of intravenous lipid emulsion, since these infusions are derived from vegetable oils, considered to be natural sources of vitamin K.

Miranda et al.[22], in a prospective controlled study, evaluated the impact of vitamin K standardization in hospital diets in 26 patients who started using warfarin with INR still outside the therapeutic range (< 2 or > 3) on the control of chronic oral anticoagulation, and 29 placebo patients with the same INR criteria. The levels of vitamin K in the free diet (200-790 µg), the soft diet (27-48 µg), and the pasty diet (14-273 µg) were quantified. After that, a diet following the daily recommendation (90 µg and 120 µg for women and men, respectively) was standardized. Patients who received the standardized diet used smaller doses of warfarin compared to the control group to reach the therapeutic range, so the use of standardized diets may help improve the prognosis of patients on warfarin.

Other interactions

In addition to vitamin K-related interactions, other dietary supplements and foods may also interact with warfarin. Warfarin is often involved in interactions due to its metabolism involving multiple active metabolic pathways[38]. Supplements such as Omega 3, ginkgo biloba, green and black teas, St. John's wort, and vitamin E, and foods like garlic and grapefruit may have significant interactions with warfarin, according to the Natural Medicine Comprehensive Database[39] (Table 3).

Table 3. Foods and supplements that interact with warfarin.

Food / Supplements	Interaction Mechanism	Reference
Garlic (*Allium sativum*)	Inhibits platelet aggregation through the compounds allicin and cysteine sulfoxide, increasing the risk of bleeding and fibrinolysis	38,40
Grapefruit	Inhibits hepatic CYP enzymes due to the presence of flavonoids, inhibiting the metabolism of R-warfarin (CYP3A4), increasing INR	12,40
Omega 3	Reduces the synthesis of cyclooxygenase (COX) and the production of thromboxanes (TXA2) by competition through the same enzymatic pathways conferring antiplatelet action, favoring an increase in the effect of warfarin	40,41
Ginkgo biloba	Induces CYP3AY by the presence of flavonoids, which can affect R-warfarin, increasing coagulation time	12,38,40,42
Green and black teas	Because of the presence of caffeine and catechins in the composition, it can inhibit COX release, TXA2 production, and clot formation; increase bleeding risk; and reduce INR	12,40
Saint John's herb	Effects of inhibition and/or induction of the P450 system, increasing the clearance of warfarin S and R. It has in its composition hypericin and flavonols that interact with warfarin increasing the metabolism of the drug	12,21,40,42
Vitamin E (≥ 300 mg/day)	Reduces the production of TXA2 by inhibiting COX activity by altering platelet aggregation functions. Vitamin E may have an inhibitory effect on vitamin K oxidation, increasing PD and INR	12,38,41,42
Fruit/ pomegranate juice	Inhibits the cytochrome P450 enzyme inhibiting the metabolism of S-warfarin (CYP2C9) and also inhibits CYP3A, increasing the risk of bleeding and increasing the INR	43,44
Cranberry juice (*Vaccinium macrocarpon*)	Favors hemorrhagic events by increasing the INR due to the presence of flavonoids that inhibit cytochrome P450 metabolism	40,43,45,46

CONCLUSION

The concentration of vitamin K varies greatly among the food groups, mainly due to the region of cultivation and other soil-climatic factors. Thus, it is important to study and construct tables of food composition that present the contents of vitamin K according to usual consumption, since it is directly related to the action of warfarin.

Although studies demonstrate that vitamin K content in food is directly related to INR, regular consumption of food sources of vitamin K is important to keep the patient within the therapeutic range of warfarin. In addition to plant foods, dietary supplements may also interact with warfarin and influence INR.

Regular monitoring of INR is the best way to protect the patient from the pharmacokinetic and pharmacodynamic interactions between warfarin and other drugs and foods.

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