Tadeusz JASIŃSKI[1]
Violetta BEDNARSKA [2]
Marian KUZMA[3]

THE STRUCTURE OF VITAMIN K AND ITS SIGNIFICANCE IN MEDICINE

Abstract: Quinones and their derivative – vitamin K are well known in medicine. The chemical structure, configurational isomerism of vitamin K and the differences in its biological activity are shown in this paper.

Keywords: vitamin K, biological activity of vitamin K, *cis-*,*trans* isomerism

1. INTRODUCTION

Vitamins are biologically active substances necessary to live. One of them is vitamin K, which in its natural form occurs as vitamin K_1 (phylloquinone), and K_2 (menaquinone), while synthetically obtained as a provitamin is vitamin K_3 (menadione). Vitamin K_2 has a much longer half-life and has better bioavailability than vitamin K_1. It is possible to determine the content of vitamin in the body of an animal on the basis of blood tests.

The research on vitamin K and its role in the function of living organisms is in constantly going development. [1, 2]. Vitamin K plays an essential role in the anti-coagulation of the blood. It also participates in the process of forming osseous tissues, carboxylation of proteins and nucleic acid metabolism. It has antibacterial and antimycotic properties. It has a high activity in the process of bone formation and also reduces the risk of the occurrence of cardiovascular diseases and calcification of blood vessels. Moreover, vitamin $K_{1,}$ as well as its derivatives, form acceptor A_1 (Photosystem I) in the electron-transfer chain in photosynthesis in green plants [3, 4]. Such a wide biochemical activity is studied in models of many redox

1 Tadeusz Jasiński, Department of Physics and Medical Engineering, The Faculty of Mathematics and Applied Physics, Rzeszow University of Technology, al. Powstańców Warszawy 6, 35-959 Rzeszów, Poland, e-mail: jasinski@prz.edu.pl
2 Violetta Bednarska, Department of Physics and Medical Engineering, The Faculty of Mathematics and Applied Physics, Rzeszow University of Technology, al. Powstańców Warszawy 6, 35-959 Rzeszów, Poland, e-mail:v.bednarska@prz.edu.pl
3 Marian Kuzma, Technical College ,State Academy of Applied Science in Przemyśl, Książąt Lubomirskich 6, 37-700 Przemyśl, Poland, mkuzma@ur.edu.pl

chains involving the transfer of electrons, which is driven by radical forms of the vitamin.

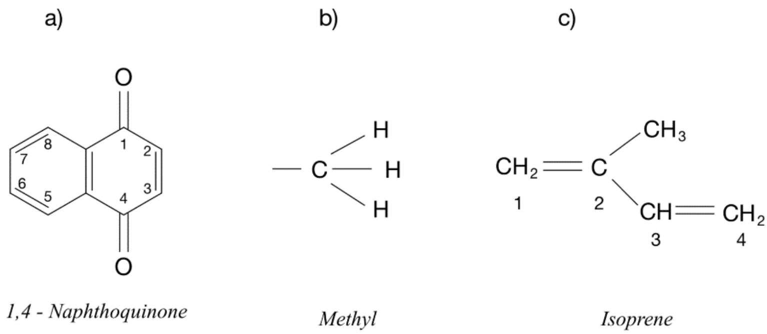
Due to its important use in medicine, Vitamin K has been intensively studied by means of various methods, including the physical methods of Electron Paramagnetic Resonance (EPR), and Nuclear Magnetic Resonance (NMR) to determine the properties of radicals and chemical structure of the vitamin [4,6].

2. CHEMICAL STRUCTURE OF VITAMIN K

Vitamin K is known as:

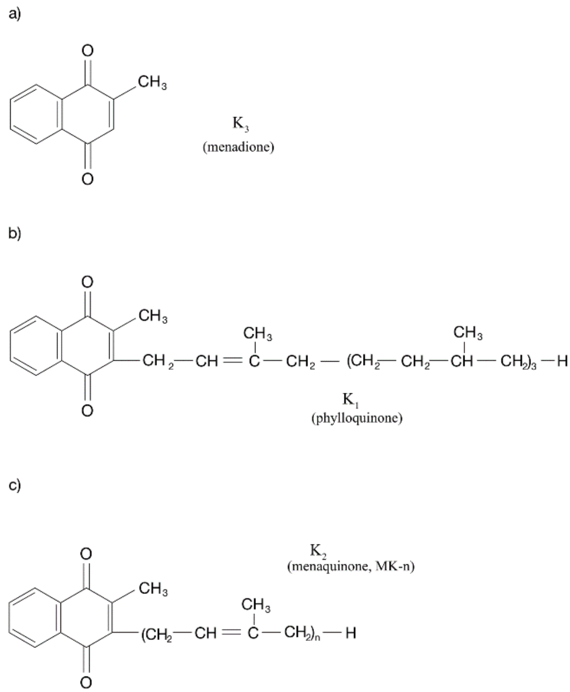
a) phylloquinone –vitamin K_1
b) menaquinone – vitamin K_2
c) menadione – vitaminK_3

The basic chemical units of vitamin K are: 1,4 naphthoquinone, methyl group (CH_3) and isoprene chain (C_5H_8)$_n$ (see Fig. 1).



Rys. 1. Podstawowe chemiczne składniki witaminy K: 1,4 naftochinon (a), grupa metylowa (b), łańcuch izoprenowy (c)
Fig. 1. Basic chemical units of vitamin K: 1,4 naphthoquinone (a), methyl group (b), isoprene chain (c)

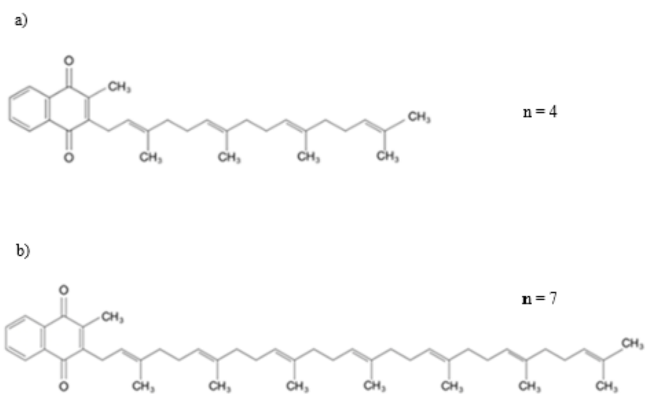
Menadione (vitamin K_3) consists of naphthoquinone and the methylene group attached to the naphthalene ring in position 2. The resulting molecule is the 2-methylo-naphthoquinone (vitamin K_3) (Fig. 2a). Menaquinone, called vitamin K_2, consists of methylonaphthoquinone and attached to it, in position 3, is a polyisoprene chain including n isoprene units (Fig. 2c). Depending on n, various forms of vitamin K_2 exist, e.g. K2MK4, K2MK7, …, K2MK10, etc.



Rys. 2. Chemiczne struktury witaminy K
Fig. 2. Chemical structures of vitamin K

3. POLYISOPRENE CHAIN OF VITAMIN K

Vitamins MK4 and MK7 (Fig. 3), are the most significant forms of vitamin K_2. Many dietary supplements offer these forms of vitamin K_2 [5, 6, 7].



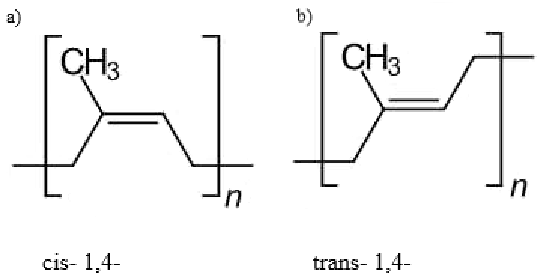
Rys. 3. Struktura menachinonu MK4 (a) i menachinonu MK7 (b)
Fig. 3. The structure of menaquinone MK4 (a), and menaquinone MK7 (b)

The main form of vitamin K contained in diet is vitamin K1 extracted from plants. It accounts for about 90% of the total content of vitamin K in diet[8]. Less common forms of vitamin K are menaquinones, which constitute about 10% of vitamin K consumed in the diet [9, 10, 11].

They are found mainly in products obtained in the process of bacterial fermentation (cheese, cottage cheese, fermented soybeans – the “natto"), or are of animal origin (offal, egg yolk, dairy products) [8, 12]. The MK-7 to MK-10 menaquinones are also produced by the bacteria in the digestive system. The MK-4 form is an exception, as it is formed by the alkenylation of menadione (K_3), or the direct conversion of phylloquinone.

4. THE CONFIGURATION OF *CIS* AND *TRANS* POLYISOPRENE CHAIN

Geometric isomerism is a phenomenon existing in chemical compounds of the same composition, including multiple bindings, yet differing in the arrangement of atoms in the molecule (Fig. 4). In the case of spatial isomerism of polyisoprene molecule, there is a possibility of different position of different substituents for each of the atoms bound by a double bond. The *cis* isomerism (Fig. 4a), occurs in the case of substituent groups which are oriented in the same direction. The *trans* isomer (Fig. 4b), occurs when the substituents are positioned on opposite sides of the double bond.



Rys. 4. Rodzaje podstawień w łańcuchu izoprenowym (a*)* *cis*- 1,4- (b) *trans*- 1,4-
Fig. 4. Types of addition in polyisoprene chains (a) *cis*- 1,4-addition, (b) *trans*- 1,4-addition

There is generally only a slight difference in the chemical properties of isomers. However, there are often differences in their physical properties, such as melting point or optical properties. Also differences in the biological activity of such isomers often are observed.

5. BIOLOGICAL ACTIVITY OF THE *CIS* AND *TRANS* ISOMERS OF VITAMIN K

Primarily, the role of vitamin K was attributed only to the process of blood coagulation. However, the results of research carried out in recent decades have indicated a wider scope of its application. It activates a number of proteins that are important for the proper functioning of an organism. In addition to the group of coagulation factors associated with the so-called blood coagulation cascade, vitamin K-dependent proteins include anticoagulants, proteins involved in bone and soft tissue mineralization and which are responsible for growth (Gas-6) [14].

The concentration of vitamin K_2 in food products is insufficient to have a medical effect. The absorption of vitamins from natural sources may be less effective with age. “Natto” (fermented soya beans), which is a traditional dish in Japan, is known as the richest source of vitamin K_2. It contains an average 1000μg/100g of MK-7 in this raw state. To obtain vitamin K_2 supplements (mainly K2MK-7), the process of soybeans fermentation using Bacillus subtilis is employed.

There is a dependency between activity and bioavailability [15, 18], and the length of the side chain and the number of double bonds (forms of vitamin K) (Table 1). Vitamin K_1 is the main form of vitamin K contained in the diet. However, it is poorly absorbed by the human body (up to 15%), and has a short half-life (1 hour). Amount of vitamin K_2 is only 10% of vitamin K present in the diet, but it is almost completely absorbed by organism.

Tabela 1. Własności różnych form witaminy K
Table 1. Properties of various forms of vitamin K

Vitamin K form	Content in the diet	Length of carbon chain	Absorption from the diet	Half-life	Daily doses
K_1	80-90%	3	weak	Few hours	
K_2 (K2MK4)	10%	4	very good	One hour	15 – 45 mg
K_2 (K2MK7)		7	very good	3 days	45 – 90 μg

Vitamin K2MK-4 requires frequent administration and high doses (45 mg per day), meaning it has a very limited application time. The lipophilic form of MK-7 has better bioavailability and a longer half-life (about 3 days). It has a higher activity in the process of osteocalcin carboxylation. The K_1 is the main vitamin K form in the diet (approx. 80-90%), however it has limited bioavailability (up to 15%) and a short half-life (few hours). K_2 form of vitamin K, the menaquinone-4 (K2MK-4) has a very good absorption, however it has a short half-life (only 1 hour), thus a frequent intake of high doses is required (15-45 mg). The next, long-chain form of vitamin K present in the diet - menaquinone-7 (K2MK-7) has a high activity, very good absorption and long half-life in the body (3 days). The use of this form of vitamin K requires low effective dose (45-90 μg), and has a strong effect on carboxylation of proteins, both in the liver (prothrombin), and outside of it (osteocalcin). K2MK-7 has a strong ability to accumulate in the blood. Because of these differences in the properties, it has been shown that to activate OC, it is enough to use MK-7 in the amount of 45-90 μg per day, while the same effect will be obtained using larger amounts of MK-4 (at least 1500 μg per day) [15 - 19].

Limited availability of K2MK-7 in the diet causes the need to supplement natural food sources. The K2MK-7 exists as geometric isomer and can occur in the *cis, trans,* and *cis/trans* forms. However, only the all-*trans* form is biologically significant and only all-*trans* isomers occur in natural diet. Various types of vitamin K2 supplements are available, mainly the ones produced using fermentation of soybeans by *Bacillus subtilis* bacteria, yet it is also produced synthetically. The production and purification methods, as well as environmental and storage conditions affect the isomer composition in the final product. Since only the *trans* form exhibits full biological activity, determining the composition of the isomers is an important issue [7].

The study of *cis* and *trans* form separation of vitamin K_1 was carried out for feeding and metabolic of rats. The lack of biological activity of the *cis* isomer of phylloquinone [20] was observed in the studies carried out. Although the *cis* isomer of phylloquinone was retained longer in liver, it was a poor substrate for 2,3-epoxidation in vivo and in vitro. This indicates that the epoxidation of vitamin K is related to its biological activity [20].

6. TRENDS IN THE GLOBAL VITAMIN K MARKET

A number of marketing companies are forecasting a significant growth in vitamin K production over the next ten years (see, for example [22]). The global vitamin K market includes food containing the vitamin, pharmaceuticals and dietary supplements.

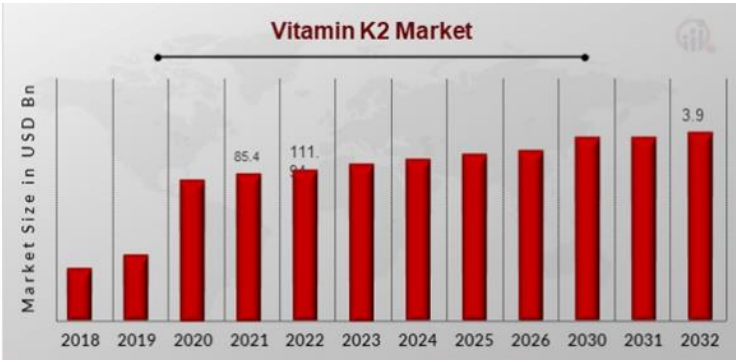
The research carried out by Nester estimates the size of the market in 2035 at USD 450 million [2]. This is an increase of 26% over the period from 2023 to 2035. The growing trend of the vitamin K market is demonstrated in the diagram shown in Fig. 5.

The market in question here will grow from USD 11 bilion in 2022 to USD 139 bilion in 2032. The average annual growth is thus 4.5%.

Such a significant growth is due to the following conditions:

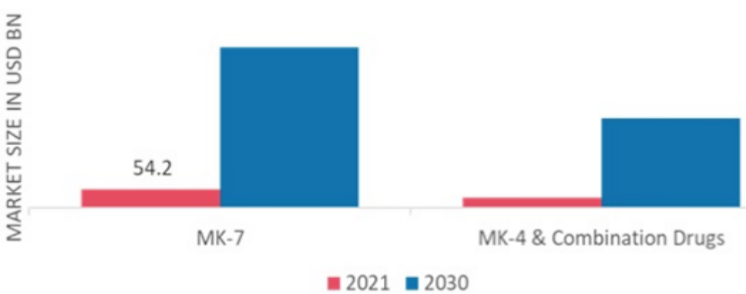
1. general demand for health-promoting foods and supplements,
2. increase in vascular disease and osteoporosis,
3. increase in the role of vitamin K in anti-cancer therapy,
4. deterioration of human skeletal health (probably due to poor quality of food), which contributes to a high number of bone fractures,
5. population growth,
6. increase in the number of ageing population,

7. increase in overall spending for pharmaceutical companies and the increase in the number of such companies,
8. better health care.



Rys. 5. Wzrost rynku witaminy K2 w okresie 2018-2032 [22]
Fig. 5. The growth of the vitamin K2 market between 2018-2032 [22]

Vitamins MK-7 and MK-4 are at the forefront of this market whose growth is shown in the graph in Fig. 6.



Rys. 6. Wzrost rynku witaminy MK-7 i MK-4 w roku 2030 [22]
Fig. 6. The growth of vitamin MK-7 and MK-4 market in 2030 [22]

Vitamin K is produced from natural raw materials (e.g. through bacterial fermentation of soybeans [23, 24, 25]). An alternative method is the chemical synthesis of this compound. Production of the vitamin from natural raw materials outweighs chemical production and this trend will continue in the future, see Fig. 7.

Rys. 3. Perspektywy rozwoju metody wytwarzania witaminy K z surowców naturalnych i metody chemicznej
Fig. 3. The prospects of the development of the method of producing vitamin K from natural raw materials and the chemical method

The largest manufacturers of vitamin K are the following companies [22]:
1. Kappa Bioscience (Norway),
2. Lessafre (France),
3. Viridis BioPharma (India),
4. Seebio Biotech (Shanghai)
5. DSM (Netherlands).

Table 2 summarizes the products (pharmaceuticals, dietary supplements) offering vitamin K available on the market in Poland.

Tabela 2. Przykładowe produkty zawierające witaminę K dostępne w Polsce
Table 2. Sample products containing vitamin K available in Poland

Name	**Composition**	**Dose Quantity**	**Price [PLN zł]**	**Manufacture**
Natural vitamin K2 forte	MK-7 in olive oil	50 µg in one drop. 900 daily servings.	31.50	Progress Labs Krakow
Vitamin K2 Mk-7 from natto	Mk-7	100 µg per tab. 120 tablets	23.99	Progress Labs Krakow
Vitamin D3+K2	MK-7	½ tab-50µg 120 tab.	21.15	SFD Opole
Witamin D3+K2-Mk7 Fort	Mk-7	15 µg	33.90	Med Future Wrocław
Multivitamina Cefarm	Vitamines C,A,D,F,K,B12	11µg per tab. 25 x 50 tab	75.00	CEFARM Mielec

7. CONCLUSIONS

Only an outline of the current knowledge about vitamin K is presented in this paper. Due to its importance in the development and functioning of living organisms, research is still ongoing. Comprehensive and long-term studies will allow for a more detailed explanation of the role of vitamin K in the development of diseases and determine the usefulness of its administration in various types of diseases.

Various biological activity of isomers of vitamin K molecules makes it necessary to identify these isomers, e.g. in pharmaceutical products. This is possible by physical methods (such as EPR, mentioned in the introduction).

This provides excellent opportunities for future research.

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STRUKTURA WITAMINY KI JEJ ZNACZENIE W MEDYCYNIE

Chinony i ich pochodne (witamina K) są dobrze znanymi cząsteczkami w medycynie. W niniejszym artykule przedstawiono strukturę chemiczną, izomerię konfiguracyjną witaminy K i różnice w aktywności biologiczne jej izomerów.

Słowa kluczowe/ Keywords: witamina K, aktywność biologiczna witaminy K, izomeria geometryczna.

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