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The multifunctional role of vitamin K_2 in biological systems

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The increasing prevalence of non-communicable diseases and an aging population are driving interest in micronutrients capable of modulating coordinated metabolic and signaling networks. Vitamin K_2 (menaquinones) is traditionally considered a cofactor of γ-glutamyl carboxylase in the vitamin K cycle, which provides γ-carboxylation of vitamin K-dependent proteins. At the same time, recent data indicate broader extrahepatic effects that link the carboxylation status of osteocalcin and matrix Gla protein to bone mineralization and vascular calcification processes, as well as pointing to potential non-carboxylation mechanisms in the regulation of redox balance, inflammation, and cellular metabolism. The aim of the study was to systematize current knowledge on the molecular mechanisms and tissue-specific effects of vitamin K_2 (mainly MK-4 and MK-7) in hemostasis, the bone-vessel axis, metabolic-endocrine regulation, immune-inflammatory responses, and neurobiology, identifying gaps in the evidence base for clinical translation. A narrative synthesis with elements of a scoping approach was performed based on a search in PubMed/MEDLINE, Scopus, and Web of Science; priority was given to randomized studies, meta-analyses, and cohort studies supported by *in vitro/in vivo* mechanistic data. Biomarkers of vitamin K functional status, in particular dp-ucMGP and uncarboxylated osteocalcin, were analyzed separately. Therefore, the effects of K_2 are context-dependent and determined by the form of menaquinone, dose, duration, and baseline vitamin K status; MK-7 is characterized by more stable pharmacokinetics and better extrahepatic carboxylation. The heterogeneity of clinical outcomes justifies the need for standardized interventions, biomarker-oriented stratification, and the selection of clinically meaningful endpoints (calcification, fractures) with parallel assessment of redox and inflammatory signaling pathways. Promising avenues include evaluating the neuroprotective potential of K_2 in well-designed studies.

Keywords: vitamin K_2; menaquinones; MK-4; MK-7; vitamin K cycle; γ-carboxylation; matrix Gla protein; vascular calcification; bone mineralization.

Introduction

Over the past decades, the burden of non-communicable diseases (cardiovascular diseases, metabolic disorders, osteoporosis, neurodegenerative conditions, and oncopathology) has been increasing against the backdrop of an ageing population and changing dietary patterns. This has prompted the search for nutrients with systemic regulatory effects that can influence enzyme cycles, cell signalling and redox homeostasis. Vitamin K_2 (menaquinones) belongs to such factors, combining classic participation in post-translational protein modification with broader extrahepatic effects important for the prevention of age-related phenotypes and comorbidity (Shearer & Newman, 2008; Mladěnka et al., 2022).

The biochemical significance of the topic is due to the fact that K vitamins form a functionally related group of quinones with different origins, transport and tissue bioavailability; for K_2, the differences between homologues (in particular MK-4 and MK-7) and their involvement in the redox cycle, which supports γ-carboxylation of vitamin K-dependent proteins (VKDP), are fundamental. It is the VKORC1/γ-glutamyl carboxylase pathway that determines the "classical" function in haemostasis, but at the same time forms a mechanistic bridge to extrahepatic targets, where the degree of carboxylation determines the bioactivity of VKDP (Oldenburg et al., 2008; Shearer & Newman, 2008).

Outside the liver, the role of K_2 in bone-mineral homeostasis and vascular biochemistry is most reasonably considered, where the carboxylation status of osteocalcin and matrix Gla protein (MGP) is associated with tissue mineralisation and calcification. An important factor is the transport of K vitamins by lipoproteins, which determines the delivery pathways of K_2 to peripheral tissues (Schurgers & Vermeer, 2002). Population data support associations between higher menaquinone intake and lower risk of coronary calcification/ischaemic heart disease, reinforcing the biochemical interpretation of the "mineral paradox" of ageing (Beulens et al., 2009; Gast et al., 2009).

At the same time, evidence is accumulating on the link between K_2 and conditions with a pronounced metabolic component (insulin resistance, dyslipidaemia) and processes where the balance of proliferation/apoptosis and redox signalling is critical. A separate layer of relevance is formed by data on the associations of K-status with oncological risks and the potential role of menaquinones in modulating cellular responses in hormone-sensitive tissues (Nimptsch et al., 2008). For practical conclusions, it is important that the longer circulation of MK-7 and its effect on extrahepatic carboxylation make this form central to discussions about the functional use of K_2 (Theuwissen et al., 2012).

At the same time, the evidence base is heterogeneous: some of the conclusions come from model systems, and clinical effects depend on the dose, duration, form of menaquinone, and baseline K status (Manna & Kalita, 2016; Mladěnka et al., 2022). The aim of this review is to systematise current knowledge about the molecular mechanisms and tissue-specific effects of K_2 (mainly MK-4 and MK-7) in haemostasis, the bone-vascular axis, metabolic-endocrine regulation, immune-inflammatory responses, and neurobiology, identifying gaps in the evidence base for clinical translation. To form practically relevant conclusions, the results are compared according to study design and relevant biomarkers, with priority given to RCT data, meta-analyses, and cohort observations. Additional relevance is provided by "non-classical" mechanisms of K_2 – interaction with nuclear re-

ceptors and signalling cascades (SXR/PXR, NF-κB, MAPK, PI3K/Akt), as well as potential effects on mitochondrial function and redox balance, which may be context-dependent for different cell types and physiological states (Puri et al., 2011; Jadhav et al., 2022; Yan et al., 2023). Accordingly, the review is structured as a synthesis of data on the chemical forms and metabolism of K_2, classical γ-carboxylation and extrahepatic targets, as well as pleiotropic cellular effects, taking into account evidence limitations (Shearer & Newman, 2008; Mladěnka et al., 2022; Dupuy et al., 2025).

Review methodology

The review was conducted as a thematic narrative synthesis with elements of a scoping approach, focused on reconciling the molecular mechanisms of vitamin K_2 action (γ-carboxylation and non-carboxyl signalling/redox effects) with data from clinical and epidemiological studies in various biological systems. Publications were searched in the PubMed/MEDLINE, Scopus, and Web of Science Core Collection bibliographic databases. Additionally, Google Scholar was used to identify relevant review articles and cross-search bibliographies (snowballing). Publications available at the time of manuscript preparation (including the latest works from the previous 5–7 years) were taken into account, with the involvement of key classical sources for describing the vitamin K cycle and VKD proteins.

The search strategy was based on the use of a combination of keywords in Ukrainian and English with logical operators (AND/OR), in particular: vitamin K2 OR menaquinone OR MK-7 OR MK-4; γ-carboxylation OR VKORC1 OR GGCX; osteocalcin OR matrix Gla protein (MGP) OR dp-ucMGP; vascular calcification; bone mineral density; inflammation OR NF-κB OR NLRP3; oxidative stress OR mitochondria; neurodegeneration OR cognition; insulin resistance OR metabolic syndrome. The review included: randomised controlled trials, meta-analyses and systematic reviews on K_2 (MK-4/MK-7); cohort and other observational studies assessing K_2 intake/status and clinical endpoints; *in vivo/in vitro* experimental studies explaining mechanisms (VKD proteins, signalling cascades, redox processes); articles containing information on K status biomarkers (dp-ucMGP, ucOC, etc.). We excluded non-peer-reviewed publications (except for selected authoritative consensus documents, if critically needed), materials without clear identification of the vitamin K form (K_1 vs K_2), studies with incomplete description of design/dosage, and duplicates.

Screening was conducted in two stages (title/abstract → full text) with the removal of duplicates. The quality of evidence was assessed descriptively, taking into account the design, risk of bias, sample size, control of confounders, and reproducibility of effects. The material was grouped by biological systems (haemostasis, bone, vessels, metabolic/endocrine effects, redox modulation, immune and neurobiological effects) and the results were compared between K_2 forms, doses, duration and baseline vitamin K status.

Chemical forms, sources and metabolism of vitamin K_2

Vitamin K is represented by two main groups of compounds: phylloquinone (K_1) of plant origin and menaquinones (K_2), which form a homologous series with different lengths of the isoprenoid chain, in particular for MK-4, MK-7, MK-8, MK-9, etc. (Fig. 1). Common to all forms is the 2-methyl-1,4-naphthoquinone "core", while the isoprenoid "tail" determines lipophilicity, transport by lipoproteins, and tissue bioavailability (Shearer & Newman, 2008; Azuma & Inoue, 2019).

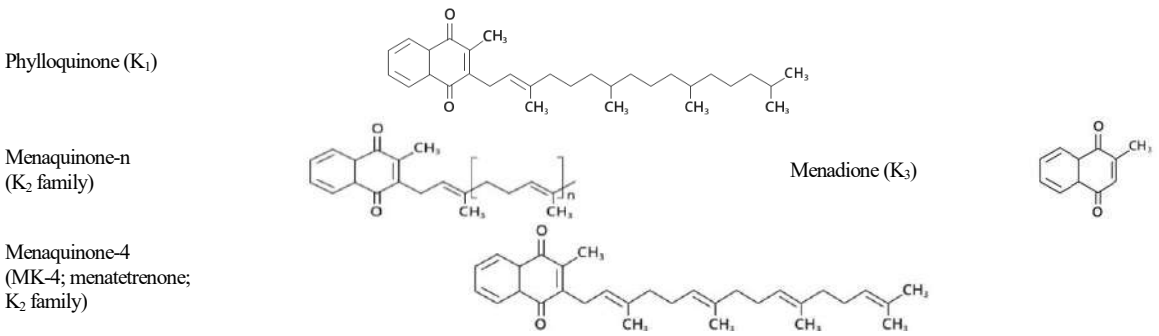

Fig. 1. Chemical structures of vitamin K

Menaquinones are obtained from food, synthesized by microbiota, and partially formed in the body through transformations, particularly for MK-4. Food sources of K2 vary according to cultural and technological traditions: fermented products (e.g., natto) are characterised by a high content of MK-7 and are considered a model for the "food" intake of long-chain menaquinones (Kaneki et al., 2001; Booth & Rajabi, 2008).

Industrial-scale biosynthesis of MK-7 is associated with *Bacillus subtilis*; fermentation conditions, control of isoprenoid pathway precursors, and product stabilisation are critical factors determining the quality of nutraceutical forms (Mahdinia et al., 2019). At the population level, assessing K_2 intake is complicated by the diversity of menaquinones and differences in food questionnaires, but it is agreed that the "Western" diet often provides lower intakes of long-chain MKs compared to diets rich in fermented foods (Booth & Rajabi, 2008).

Clinical and epidemiological observations link higher dietary intake of menaquinones with a lower risk of certain chronic conditions. In particular, cohort studies have reported associations between high K_2 intake and lower severity of coronary calcification or frequency of coronary events (Beulens et al., 2009; Gast et al., 2009). Some data also relate to cancer risks, including prostate cancer, which highlights the need for accurate differentiation between K_1 and K_2 forms and control of confounders (Nimptsch et al., 2008). After absorption in the small intestine, menaquinones are incorporated into chylomicrons and then redistributed between lipoprotein fractions, which accounts for the difference between hepatic and extrahepatic vitamin K pools. It has been shown that K vitamins have different transport pathways, and long-chain menaquinones are more associated with fractions that deliver to extrahepatic tissues (Schurgers & Vermeer, 2002).

An important pharmacokinetic aspect is the contrast between MK-4 and MK-7: MK-7 is characterised by a longer half-life and a more stable increase in circulating concentrations, which potentially facilitates the maintenance of carboxylation of extrahepatic Gla proteins. Comparative data in healthy women demonstrate different bioavailability and K-status marker profiles for MK-4 and MK-7 (Sato et al., 2012).

Vitamin K metabolism involves redox transformations (quinone ↔ hydroquinone ↔ epoxide) within the vitamin K cycle, which allows for the repeated use of the γ-carboxylation cofactor.

At the cellular level, this cycle is integrated with the work of the endoplasmic reticulum and reductase systems that restore the active form; disruption of the cycle underlies the effects of vitamin K antagonists (Shearer & Newman, 2008).

In the context of biological systems, it is appropriate to consider K_2 as a metabolic "hub" that combines dietary sources, microbial contributions, lipoprotein transport, and cellular redox transformations. This integration creates the conditions for multidirectional extrahepatic effects, which are revealed through the activation of K-dependent proteins and non-carboxyl signalling actions (Jadhav et al., 2022).

Molecular mechanisms of vitamin K_2 action

The molecular effects of vitamin K_2 are conventionally divided into carboxyl (classical) and non-carboxyl (pleiotropic) mechanisms, which are implemented in different tissues and at different levels of regulation (Yan et al., 2023). Their combination forms a systemic phenotype: from maintaining haemostasis and bone mineralisation to modifying vascular calcification, inflammation and cell viability (Mladěnka et al., 2022).

The classical pathway is based on the participation of the reduced form of vitamin K (hydroquinone) as a cofactor for γ-glutamyl carboxylase, which converts certain glutamate residues to γ-carboxyglutamate (Gla) in vitamin K-dependent proteins (VKDP) (Fig. 2). During the reaction, vitamin K is oxidised to epoxide, and its regeneration is ensured by the enzymatic chain of the vitamin K cycle (VKORC1 and related reductases), which supports the "recycling" of the coenzyme and determines the proportion of carboxylated forms of VKDP in hepatic and extrahepatic tissues (Oldenburg et al., 2008).

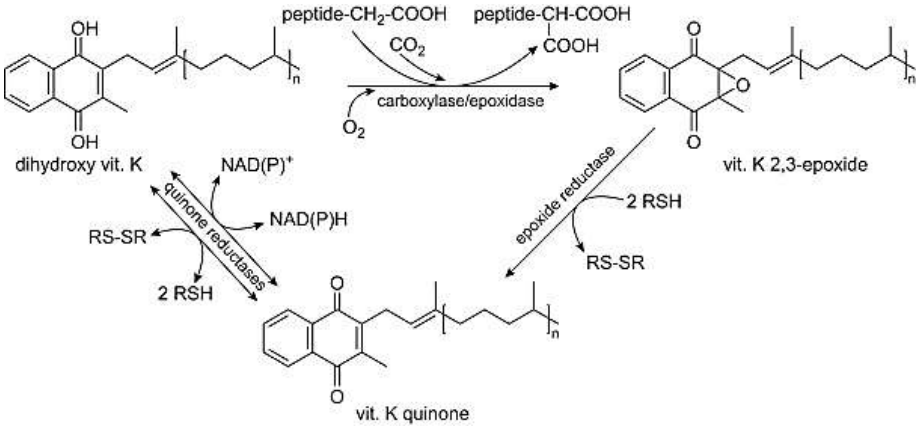

Fig. 2. Cyclic mechanism of action of vitamin K

The effectors of γ-carboxylation are coagulation factors and extrahepatic Gla proteins, in particular osteocalcin, matrix Gla protein (MGP), Gas6 and protein S. Extrahepatic proteins are characterised by a higher proportion of non-carboxylated forms under normal conditions, which emphasises the importance of K_2 availability in the relevant tissues and the sensitivity of peripheral regulatory circuits to subclinical deficiency (Mladěnka et al., 2022). From a practical point of view, the ratio of carboxylated and non-carboxylated forms of VKDP reflects the availability of K_2 in tissues.

In the vascular wall, activated MGP binds hydroxyapatite crystals and limits the osteogenic transdifferentiation of smooth muscle cells; an increase in circulating dp-ucMGP is considered a marker of functional vitamin K deficiency and an increased risk of calcification (Hariri & Bell, 2021). In bone tissue, the degree of osteocalcin carboxylation correlates with K status indicators and reflects the biochemical "readiness" of the matrix for physiological mineralisation.

Non-carboxyl effects of K_2 include interaction with nuclear receptors and modulation of signalling cascades that control inflammation, proliferation, apoptosis, and metabolic adaptation. The involvement of NF-κB, MAPK, and PI3K/Akt pathways and Gas6/Axl signalling has been described, providing tissue-specific effects beyond γ-carboxylation (Jadhav et al., 2022; Yan et al., 2023). Separately, the binding of K_2 and its analogues to the steroid and xenobiotic receptor SXR/PXR and the induction of biotransformation gene expression (in particular CYP3A4) have been demonstrated, forming a bridge between nutrient regulation and xenobiotic metabolism (Puri et al., 2011).

A comparison of MK-4 and MK-7 shows that different lengths of the isoprenoid chain are associated with different pharmacokinetic profiles and, presumably, different durations of extrahepatic K status maintenance. In a clinical model of healthy women, MK-7 provided a more sustained increase in circulating levels and markers of extrahepatic carboxylation compared to MK-4 (Sato et al., 2012).

The functional consequences of Gla-protein signalling extend beyond structural mineralisation: Gas6 and protein S are involved in the regulation of cell survival, apoptosis and immune responses, explaining the potential links between K status and inflammatory-degenerative phenotypes (Wen et al., 2018).

Beyond carboxylation, menaquinones are considered redox-active naphthoquinones capable of modulating mitochondrial electron transport function and energy yield. It has been experimentally shown that vitamin K_2 can act as a mitochondrial electron carrier in models of mitochondrial dysfunction, supporting electron transport and ATP production (Vos et al., 2012). Consistent with this, delivery of the reduced form MK-4 (menaquinone-4) in a cellular model partially atenuated the toxic effects of complex I inhibitor (rotenone), interpreted as a supportive effect on mitochondrial function (Toki et al., 2022).

In summary, the effects of K_2 should be considered as two interrelated blocks: maintenance of vitamin K-dependent post-translational modification of VKDP through the functioning of the vitamin K cycle; carboxylation-independent participation of menaquinones in the regulation of mitochondrial function, redox status, and metabolic plasticity. This multi-level architecture of mechanisms explains the multifunctional effects of K_2 in various organs and physiological circuits (Yan et al., 2023).

The classic role of vitamin K_2: the haemostasis system

The classic, historically first established function of vitamin K, including menaquinones (K_2), is its participation in haemostasis as an essential cofactor for γ-carboxylation of plasma coagulation proteins. Vitamin K-dependent (VKD) factors include II (prothrombin), VII, IX, X, as well as the natural anticoagulants Protein C, Protein S and Protein Z (Hao et al., 2020; Mathews & Hayward, 2025). Their N-terminal Gla domains (γ-carboxyglutamate) provide Ca^{2+} binding and fixation to cell phospholipid membranes, which is necessary for the assembly and spatially organised functioning of the coagulation cascade (Furie et al., 1999; Hao et al., 2020).

The molecular basis for this role is the vitamin K cycle, which supports the regeneration of the active hydroquinone form for γ-glutamyl carboxylase (GGCX): during carboxylation, an epoxide is formed, which is recycled by VKORC1 (vitamin K epoxide reductase complex subunit 1) back to the quinone form with subsequent restoration to hydroquinone (Oldenburg et al., 2008; Shearer et al., 2014). Functionally, this circuit ensures the repeated use of a small pool of vitamin K, maintaining the stability of γ-carboxylation under conditions of fluctuating dietary intake. GGCX operates in the membrane environment of the endoplasmic reticulum, coordinating the interaction of vitamin K, substrate glutamate, O_2, and CO_2 within the enzyme complex (Hao et al., 2020). Therefore, in the liver, the K cycle is a critical "enzyme amplifier" of coagulation function: without it, the synthesis of VKD proteins is not transformed into their biological activity.

Fundamental research by Furie et al. (1999) has shown that it is the Gla domains that determine the ability of VKD factors to form Ca^{2+}-dependent complexes (tenase, prothrombinase) on the surface of activated platelets and membranes (Furie et al., 1999). In the absence of γ-carboxylation, proteins are synthesized but remain functionally

defective: they do not bind Ca^{2+} and are not localized on phospholipid platforms, which blocks the effective assembly of protease coagulation complexes (Hao et al., 2020). Clinically, this is reflected in prolonged PT, increased INR, and decreased activity of factors II, VII, IX, and X (Mathews & Hayward, 2025).

Although hepatic coagulation function is primarily maintained by phylloquinone (K_1), menaquinones (K_2) are also involved in the vitamin K cycle and may be effective cofactors for GGCX in the liver (Shearer et al., 2014). From a coagulation perspective, K_1 and K_2 are interchangeable, as it is the total pool of the reduced form that is critical, not the source of the vitamin (Halder, 2019). However, menaquinones differ in their pharmacokinetics (longer half-life, different lipoprotein transport, different tissue distribution), which explains their greater importance for stable carboxylation of extrahepatic Gla proteins in the long term. In particular, MK-7 is more often associated with the maintenance of MGP and osteocalcin, while adequate K1 supply is usually sufficient for hepatic coagulation (Shearer et al., 2014).

Vitamin K (K_1 or K_2) deficiency reduces the activity of VKD factors and causes bleeding (skin, mucous, internal), bleeding from injection sites/postoperative wounds; in newborns, haemorrhagic disease of the newborn may develop (Mathews & Hayward, 2025; Mathews et al., 2025). Laboratory deficiency is characterised by prolonged PT/INR, decreased activity of factors II, VII, IX, X, and increased non-carboxylated prothrombin (PIVKA-II) as a sensitive marker of functional deficiency (Mathews & Hayward, 2025). The most common causes are cholestasis and fat malabsorption, prolonged antibiotic therapy, severe malnutrition, and lack of prophylactic vitamin K administration to newborns.

An important clinical aspect is the interaction with vitamin K antagonists (primarily warfarin): inhibition of VKORC1 blocks K recycling and, accordingly, γ-carboxylation of VKD factors (Shearer et al., 2014). A classic study by Weiss et al. showed that at the beginning of therapy, Protein C and Protein S (shorter half-life) decrease faster than prothrombin and other coagulation factors (Weiss et al., 1987). This creates a temporary "window" of relative hypercoagulation with a risk of thrombosis (including warfarin-induced skin necrosis), requiring careful dose titration and, if indicated, initial "bridging" therapy with parenteral anticoagulants (Weiss et al., 1987).

Reviews of vitamin K metabolism emphasise that warfarin reduces γ-carboxylation not only of hepatic factors but also of extrahepatic Gla proteins (MGP, osteocalcin) (Shearer et al., 2014). Pathophysiologically, this creates the conditions for the progression of vascular calcification and negative changes in bone tissue with prolonged use, even with adequate INR control. On the other hand, clinical observations show that low stable doses of vitamin K can reduce INR variability, making it easier to achieve the therapeutic range without losing the target anticoagulation level (Rombouts et al., 2007). Importantly, this approach requires individualisation (dietary habits, comorbidities, etc.).

Vitamin K_2 and bone mineral homeostasis

In bone mineral homeostasis, vitamin K_2 provides γ-carboxylation of bone-associated Gla proteins, converting them into active Ca^{2+}-binding forms that can interact more effectively with the mineral phase of bone (Fig. 3). This mechanism is associated with changes in remodelling, BMD parameters, fracture risk, and regulation of extraosseous calcification within the "bone-vascular axis" (Wasilewski et al., 2019; Capozzi et al., 2020).

The key effector in bone is osteocalcin of osteoblast origin: the carboxylated form has a higher affinity for hydroxyapatite. K_2 status is reflected by the fraction of uncarboxylated osteocalcin and markers of bone metabolism; for MK-7, this has been demonstrated in long-term placebo-controlled studies in postmenopausal women (Knapen et al., 2013).

Clinical data on K_2 and BMD are most complete in postmenopausal women. For MK-4 at a pharmacological dose of 45 mg/day (mainly studies in Japan), a slowing of BMD loss and a reduction in fracture rates have been described, with parallel changes in bone remodelling markers (Shiraki et al., 2000; Sato et al., 2005; Inoue et al., 2009; Iwamoto et al., 2013; Iwamoto et al., 2014). The results should be interpreted taking into account the differences in protocols. For MK-7, relevant nutritional doses: MK-7 (180 μg/day) was associated with a slowdown in age-related BMD loss and improved bone strength parameters with a shift in osteocalcin status (Knapen et al., 2013). The effect on fractures is considered less certain due to the heterogeneity of endpoints (Zhang et al., 2022).

Meta-analyses generally confirm the moderate benefit of K_2 on BMD and biomarkers, which depends on the form (MK-4/MK-7), duration, and baseline vitamin K status; a meta-analysis by Xie et al. (2024) showed a statistically significant improvement in BMD in a number of locations (Capozzi et al., 2020).

The synergy between vitamins D and K_2 is that D induces the synthesis of osteocalcin and MGP and enhances calcium metabolism, while K_2 provides their functional "activation" through carboxylation. Within the "D-K-calcium" axis, this supports bone mineralisation and limits extraosseous calcification (Schwalfenberg, 2017; van Ballegooijen & Beulens, 2017; Wasilewski et al., 2019).

Disturbances in bone mineral homeostasis are more common in malabsorption and chronic diseases: in inflammatory bowel diseases, a decrease in BMD has been described in combination with K and D deficiency and changes in bone metabolism markers (Roenn et al., 2016; Khalil et al., 2021). In chronic kidney disease/dialysis, low K_2 status and elevated non-carboxylated Gla proteins are often found, which are associated with impaired mineral metabolism and calcification tendency (Fusaro et al., 2017).

Vitamin K antagonists are also important: warfarin therapy is associated with an increased risk of fractures, consistent with the blockade of osteocalcin and MGP carboxylation (Veronese et al., 2015).

In summary, K_2 (MK-7 in nutritional doses and MK-4 in pharmacological doses) is a biochemical modifier of bone mineral metabolism through γ-carboxylation of Gla proteins and interaction with vitamin D. The evidence supports a reproducible but moderate benefit in preserving BMD in at-risk groups and the need for further standardised studies with clinically relevant endpoints (Capozzi et al., 2020; Xie et al., 2024).

Vitamin K_2 and the vascular system

In the vascular wall, vitamin K_2 should be treated as a biochemical cofactor of γ-carboxylation of extrahepatic Gla proteins, which inhibit ectopic mineralisation. The key effector is MGP: in its carboxylated state, it binds Ca^{2+} and interacts with calcium phosphate phase nuclei, reducing nucleation and growth of hydroxyapatite in the arterial media (Schurgers et al., 2008; Cranenburg et al., 2009; Hariri & Bell, 2021). Insufficient carboxylation shifts the balance towards inactive forms of MGP and weakens its anti-crystallisation potential.

From the perspective of analytical biochemistry, dp-ucMGP is an integral marker that reflects the availability of menaquinones, the intensity of their use in carboxylation reactions, and the dynamics of vascular matrix remodelling (Dalmeijer et al., 2013; Chatrou et al., 2018; Vossen et al., 2021). In this interpretation, an increase in dp-ucMGP means that a significant proportion of MGP remains chemically "inactive".

The bioavailability of K_2 for the vascular wall depends on lipoprotein transport and tissue distribution of K vitamins. Lipoprotein transport pathways and competition between hepatic and extrahepatic pools create a situation where coagulation-oriented supply can coexist with relative insufficiency of carboxylation of matrix Gla proteins in peripheral tissues (Spronk et al., 2003; Schurgers et al., 2004). Additionally, the contribution of intracellular reductase systems to maintaining the active form of vitamin K is discussed (Scheiber et al., 2015).

Experimental models of calcification are consistent with the fact that K_2-dependent activation of MGP alters the local chemistry of the matrix (calcium binding, supersaturation with calcium phosphate salts) and the mechanical properties of the arterial wall through the remodelling of the elastin-collagen framework (Wasilewski et al., 2019; Villa-Bellosta, 2020; Vossen et al., 2020).

The context of chronic kidney disease and haemodialysis is indicative of the "$K_2 \rightarrow$ MGP" axis, as uraemic conditions exacerbate calcification load and are accompanied by an increase in dp-ucMGP;

in this direction, dp-ucMGP and vascular stiffness parameters are used as sensitive intermediate biomarkers of K-status change (Caluwé et al., 2014b; Evenepoel et al., 2014; Evenepoel et al., 2015; Oikonomaki et al., 2019).

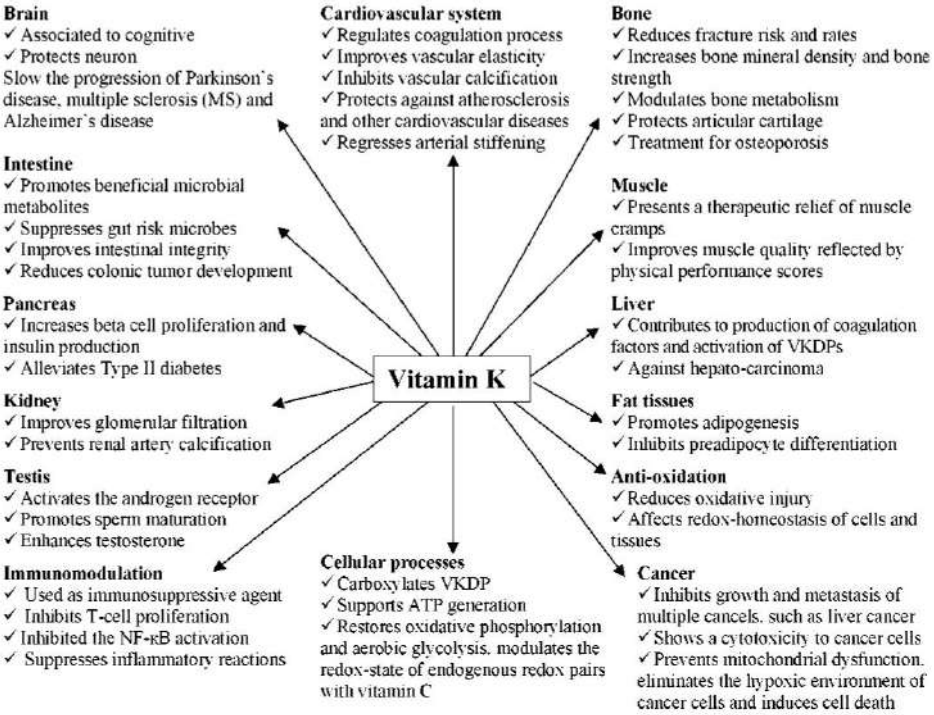

Fig. 3. Functions of VK in multiple-organ systems

In long-term protocols in postmenopausal women, MK-7 is interpreted as a factor that increases the proportion of carboxylated extrahepatic Gla proteins; in this approach, the dynamics of dp-ucMGP and related markers play a key role (Theuwissen et al., 2012; Sato et al., 2020). In summary, the effect of K_2 on the vascular system can be correctly presented through the axis "menaquinone availability → carboxylation → active MGP → reduction of calcium-phosphate crystallisation prerequisites.

Redox-modulating, antioxidant and cellular processes of vitamin K_2

Vitamin K_2 (menaquinones) are lipophilic quinone compounds whose action manifests itself in two interrelated areas: participation in the enzymatic γ-carboxylation pathway of vitamin K-dependent proteins (VKDP) and non-carboxyl effects on cellular processes mediated by the redox properties of the quinone nucleus and membrane localisation. This "dual perspective" allows K_2 to be considered a modifier of cellular plasticity, where the direction of the effect is determined by the tissue context and the form of menaquinone (Yan et al., 2023). The key point of integration remains the maintenance of the reduced form of vitamin K in the K-vitamin cycle, which ensures the functional activity of VKDP in different compartments (Mladěnka et al., 2022).

The redox-modulating prerequisites of K_2 are associated with incorporation into lipid membranes and potential involvement in electron transfer. Model membrane systems have shown that MK-4, MK-7, and MK-9 homologues differ in their acid-base and redox characteristics, which may affect their action in membranes and the efficiency of electron transfer (Dharmaraj et al., 2020). A generalisation of the mechanisms highlights the interaction of K_2 with membrane redox pairs and its possible role in stabilising mitochondria as a key "hub" of cellular energy and ROS signalling (Ivanova et al., 2018).

In the context of cellular bioenergetics, menaquinones are considered molecules capable of maintaining electron flows and, under certain conditions, improving energy metabolism parameters (ATP generation, oxidative phosphorylation efficiency). The effects described in model objects are consistent with the restoration of mitochondrial functions in cases of impaired electron transport, accompanied by the normalisation of energy indicators and a decrease in stress markers (Vos et al., 2012). This is consistent with review data on the role of K_2 in cellular metabolism and mitochondrial biology (Toki et al., 2022) and supports the interpretation of redox activity and membrane localisation as complementary factors capable of correcting OXPHOS disorders and associated metabolic shifts (Vos et al., 2012; Toki et al., 2022). The antioxidant effects of K_2 should be interpreted as a consequence of redox modulation rather than as "direct" universal radical scavenging. It has been shown that K vitamins can prevent oxidative cell death by inhibiting 12-lipoxygenase, limiting ROS-dependent damage cascades (Li et al., 2009). At the biochemical level, this is consistent with the idea of K_2 as a modifier of the redox threshold of the cell, capable of stabilising membrane potential, inhibiting excessive ROS accumulation and supporting endogenous antioxidant systems (Ivanova et al., 2018). At the same time, the effects of K_2 are context-dependent: in transformed cells, redox shift can serve as a trigger for apoptotic programmes, while in non-transformed tissues, cytoprotective scenarios are more common (Yan et al., 2023). This highlights the need to differentiate between models, doses, and forms of menaquinone when interpreting "antioxidant" conclusions (Ivanova et al., 2018).

The redox functions of menaquinones are clearly demonstrated in microbial systems, where K_2 is a canonical electron carrier. In particular, menaquinone turnover in the cytochrome bd system of *Mycobacterium tuberculosis* is modulated by the redox state of Q-loop elements, emphasising the dependence of menaquinone-dependent electron pathways on local structural redox switches (van der Velden et al., 2025).

Thus, K_2 integrates the classical pathway (γ-carboxylation of VKDP) with redox-controlled mechanisms that affect mitochondrial function, energy balance, and ROS signalling parameters; for biochemically correct conclusions, comparisons of homologues (Dharmaraj et al., 2020) and reproducible metrics of bioenergetics/redox state in adequate model systems (Vos et al., 2012; Toki et al., 2022) remain fundamental.

Immunomodulatory and anti-inflammatory properties of vitamin K_2

Accumulated experimental data indicate that vitamin K_2 (mainly MK-4 and MK-7) is not only a cofactor for γ-carboxylation of Gla

proteins, but also a modulating factor of inflammatory and immune signalling pathways. In cellular and animal models, K_2 affects key nodes of the inflammatory response (NF-κB, NLRP3 inflammasome, MAPK and PI3K/Akt cascades) and is associated with a reduction in oxidative-nitrosative stress (ROS/NO, iNOS, COX-2). Together, this manifests itself in the suppression of pro-inflammatory cytokine synthesis (in particular TNF-α, IL-1β, IL-6) and partial normalisation of functional responses in both immunocompetent and parenchymal cells.

The NF-κB cascade is considered to be the central target for the anti-inflammatory action of K_2. In various cell systems (MC3T3-E1 osteoblasts, HepG2 hepatocytes/cells, monocyte macrophages, vascular smooth muscle cells, etc.), MK-4 and MK-7 inhibit NF-κB activation and pro-inflammatory gene transcription (Pan et al., 2016; Li et al., 2018; Wu et al., 2019; Hariri & Bell, 2021). For monocyte macrophages, a dose-dependent reduction in TNF-α, IL-1β, and IL-6 has been described under the influence of MK-4/MK-7, along with inhibition of NF-κB-dependent transcription (Pan et al., 2016). Similar effects have been reported for HepG2 cells and MC3T3-E1 osteoblasts, where MK-4/MK-7 reduced NF-κB activity and the expression of pro-inflammatory mediators (Hitomi et al., 2005; Wu et al., 2019). It is important to note that for vascular cells and macrophages, the described effects occur at lower concentration ranges, accompanied by a decrease in IL-6/TNF-α, ROS and COX-2 production and, accordingly, a reduction in oxidative-inflammatory stress in the vascular wall.

In addition to NF-κB, K_2 is capable of modulating NLRP3 inflammasome, MAPK (ERK, p38, JNK) and PI3K/Akt pathways with a subsequent decrease in iNOS/COX-2 expression and NO/ROS formation. From a biochemical point of view, this is important because NLRP3 activation is associated with IL-1β maturation, and MAPK/PI3K-Akt provide "amplifiers" for inflammatory transcription programmes and stress responses. In hepatocyte and macrophage models, MK-4/MK-7 combined NF-κB inhibition with a reduction in ROS, IL-6, TNF-α, and iNOS, which correlated with a reduction in metabolically associated inflammation and improved insulin sensitivity (Li et al., 2018). Thus, K_2 can be interpreted as a biochemical modifier of inflammatory cascades that acts both at the level of signalling "switches" and at the level of effector enzymes of oxidative stress.

Importantly, the anti-inflammatory effects of K_2 manifest at the intersection of inflammation, tissue remodelling, and cell proliferation. In osteoblastic models, MK-4/MK-7, along with NF-κB inhibition, modulated the ratio of osteoprotegerin to RANKL, reducing osteoclasogenesis and bone resorption (Badmaev et al., 2011; Wu et al., 2019). In osteoclastic systems, MK-7 limited RANKL-dependent osteoclast activation with a decrease in NF-κB activity, ROS, and IL-1β (Badmaev et al., 2011). In hepatocellular carcinoma cells, MK-4 demonstrated an antiproliferative effect through cell cycle regulation (cyclins/Cdk, p21/p27) against a background of reduced NF-κB activity and redox stress (Hitomi et al., 2005; Al-Suhaimi et al., 2014). This combination of anti-inflammatory and anti-proliferative properties is conceptually significant in the context of chronic inflammation, remodelling and potential carcinogenesis.

Particular attention is drawn to data on the neuroimmune modulatory effect of K_2. Roumeliotis' summary describes that MK-4 in the SK-N-BE neuroblastoma line inhibits NF-κB, reduces IL-1β/IL-6 expression, and can modulate epigenetic mechanisms (methylation/acetylation of genes associated with inflammation and neurodegeneration). In the same context, the anti-ferroptotic potential of MK-4 is noted due to the reduction of iron-dependent lipid peroxidation (Roumeliotis et al., 2025a), which is relevant for neuroinflammatory conditions with pronounced redox imbalance. Additionally, in neuronal models, K_2 has been associated with reparative effects (particularly remyelination) and suppression of the NF-κB-dependent response through the activation of Gas6/Axl signalling. γ-carboxylation of Gas6/Protein S may affect TAM receptors (Tyro3, Axl, Mer), efferocytosis, and inflammation resolution (Mehta et al., 2017).

An additional regulatory circuit is the SOCS/STAT axis as a negative regulator of JAK/STAT signalling: SOCS proteins limit excessive or chronic activation of inflammation (Emanuelli et al., 2000). Although the direct interaction of K_2 with the SOCS system has been described only to a limited extent, the reduction of IL-6 (as a key activator of STAT3-dependent programmes) and the inhibition of NF-κB suggest an indirect effect of K_2 on STAT-dependent transcription and the maintenance of negative feedback in metabolic inflammation (Li et al., 2018).

In summary, the immunomodulatory and anti-inflammatory effects of K_2 are best explained by its complex action on transcriptional regulators (primarily NF-κB), NLRP3/MAPK/PI3K-Akt signalling cascades, and oxidative-nitrosative stress effectors (iNOS/COX-2, ROS/NO). Most of the evidence comes from *in vitro/in vivo* models; therefore, studies directly evaluating the effect of K_2 on systemic inflammatory markers and immune status in humans are needed for translation into clinical recommendations. At the same time, the presence of clear molecular targets has sparked interest in K_2 as a potential nutraceutical modifier of chronic inflammation in cardiometabolic, neurodegenerative, and osteoarticular contexts.

Osteocalcin is sometimes considered an additional "bridge" between bone and metabolic circuits: its undercarboxylated form (uOC) exhibits endocrine effects, including effects on pancreatic β-cells and tissue sensitivity to glucose.

Endocrine and metabolic effects of vitamin K_2

The endocrine and metabolic effects of vitamin K_2 should be considered as a consequence of the interaction of menaquinones with energy and lipid metabolism circuits, which is determined by the functional state of vitamin K-dependent proteins, redox- and inflammation-induced changes in signalling, and the bioavailability of MK-4/MK-7. A synthesis of experimental and nutritional data allows K_2 to be considered a modifier of metabolic plasticity in the bone-vessel-muscle-liver system, but the scale of the effects depends on the initial K status and study design (Manna & Kalita, 2016). Associations of K status with cardiometabolic markers support the feasibility of biochemical analysis of this circuit (Popa et al., 2021). In the context of metabolic prevention, K_2 is also associated with glycaemic and lipid phenotypes and their molecular determinants (Zhang et al., 2023).

The biochemical basis for such interpretations is the γ-carboxylation of vitamin K-dependent proteins in extrahepatic tissues, primarily osteocalcin, whose functional fractions are associated with metabolic responses. Osteocalcin is considered a possible link between bone mineral homeostasis and carbohydrate metabolism regulation, so the distinction between carboxylated and non-carboxylated forms is fundamental (Choi et al., 2011). In this context, the effect of K supplementation on insulin sensitivity should not be interpreted as a direct "hormonal" effect: rather, it is a modification of protein and signalling circuits that integrate mineral and energy metabolism (Manna & Kalita, 2016; Popa et al., 2021). The correlation between K status, glucose metabolism indicators and other markers is interpreted as a multifactorial phenomenon against the background of dietary, inflammatory and microbiotic influences (Choi et al., 2011; Popa et al., 2021; Zhang et al., 2023).

The endocrine "field" of K_2 includes changes in markers reflecting the regulation of adipose tissue and systemic metabolism (adipokines, low-grade inflammation, components of calcium-phosphate metabolism), however, review summaries emphasise the predominance of indirect mechanisms through protein effectors and signalling cascades (Bellone et al., 2022; Lai et al., 2022). For contexts of obesity/metabolic disorders, associations of K status or K interventions with glycaemic control and endocrine markers have been described; interpretation requires a clear distinction between vitamin K forms and associated nutrient factors (Rahimi Sakak et al., 2021).

The summary of interventional data on metabolic endpoints (fasting glucose, insulin, HOMA-IR, HbA1c) is mainly formed by systematic reviews and meta-analyses, which highlight the heterogeneity of studies and differences in vitamin K form and participant characteristics (Suksomboon et al., 2017). Generalisations suggest that the effects may be moderate and context-dependent and do not show a stable "universal" trend (Shahdadian et al., 2018). At the same time, meta-analytic assessments indicate possible subgroup benefits for insulin resistance indicators under certain protocols, requiring stratification by K form, duration, nutrient status, and concomitant dietary

components (Suksomboon et al., 2017; Shahdadian et al., 2018). RCTs focusing on metabolic markers remain a key source of causal conclusions, especially in samples with impaired glycaemic homeostasis (Li et al., 2023).

The molecular and cellular mechanisms discussed in relation to the metabolic effects of K_2 include modification of insulin-sensitive cascades, support of mitochondrial function, and control of redox signalling in metabolically active tissues. In muscle models, K_2 has been described to participate in the regulation of glucose transport via PI3K/Akt and GLUT4 pathways (Su et al., 2021). Some studies consider K_2 as a modifier of insulin resistance in the context of muscle dysfunction and energy metabolism, with an emphasis on mitochondrial parameters and transcriptional responses (Zhang et al., 2025). Comparative interpretations for MK-7 in these models link cellular metabolism to nuclear receptor and signalling pathways (Su et al., 2021; Zhang et al., 2025).

Lipid metabolism and hepatic phenotypes (steatosis/NAFLD) form a separate cluster, where K_2 is considered in relation to transcriptional regulation, oxidative balance, and inflammatory signals. Review summaries describe potential associations between K_2 and lipid markers, including markers of liver function and risks of metabolic syndromes (Zhang et al., 2023; Dupuy et al., 2025). Observational data support the need for validation of K-status biomarkers in metabolic cohorts (Popa et al., 2021). Broader cardiometabolic generalisations highlight the dependence of conclusions on design, assessment tools, and background nutrition (Simes et al., 2019; Dupuy et al., 2025), while early evidence emphasises the need to control for confounding factors (Dam et al., 2015). Integrative muscle-liver schemes highlight the possibility of coordinating insulin sensitivity and lipid metabolism mechanisms within a single metabolic framework (Su et al., 2021; Zhang et al., 2025).

The endocrine-metabolic profile of K_2 should be interpreted in the broader context of cellular programmes, where metabolism, redox status and inflammation intersect with growth regulation. Reviews emphasise that lipid metabolism is structurally linked to oncogenic signalling, so data on K_2-induced modification of cascades are also informative for metabolic regulation (Khan et al., 2024). Oncologically relevant models describe the control of inflammatory and redox cascades (NF-κB, MAPK, mitochondrial responses), which are also key to cellular metabolic adaptation (Xv et al., 2018; Welsh et al., 2022). The synergistic effects of K_2 in combination with calcitriol-dependent responses emphasise the role of transcriptional programmes (Narvaez et al., 2023). The mechanisms described include suppression of NF-κB-dependent cell cycle regulation (Ozaki et al., 2007) and ROS- and MAPK-related responses (Duan et al., 2016). Review data further emphasise context dependence: redox activity can maintain homeostasis in non-oncogenic systems and trigger stress cascades in transformed cells (Ivanova et al., 2018).

Neurobiological effects and potential neuroprotective potential

Vitamin K_2 is often considered a neuroactive micronutrient with potential neuroprotective effects on the brain. In the nervous system, K_2 performs interrelated functions: it ensures γ-carboxylation of neuronal Gla proteins (Gas6, Protein S), regulates sphingolipid metabolism, influences mitochondrial homeostasis, neuroinflammation and ferroptosis, and indirectly modulates the risk of vascular cognitive impairment (Ferland, 2012).

In brain tissues, the main form of vitamin K is MK-4, but evidence suggests that dietary MK-7 (particularly from fermented foods) is able to cross the blood-brain barrier, accumulate in the brain, and be stored longer due to its extended half-life (Popescu & German, 2021). The transport of K vitamins in the CNS occurs mainly in the form of lipoproteins, with the participation of SR-B1 class receptors and apolipoproteins, which facilitates the uptake of menaquinones by neurons and glial cells. Intracellularly, MK-4/MK-7 are reduced to menaquinol, which can act as an electron carrier in the mitochondrial respiratory chain and serves as a substrate for γ-glutamyl carboxylase, which is necessary for the activation of Gas6 and Protein S (Ferland, 2012). One of the key links in the action of K_2 is Gas6/Protein S–TAM signalling (Tyro3, Axl, Mer), which regulates neuron survival, remyelination, and microglial response. Experimental models show that only γ-carboxylated forms of Gas6 and Protein S are full-fledged ligands for TAM receptors, so sufficient K_2 supply is critical for effective activation of this pathway (Ferland, 2012). Stimulation of Gas6/TAM signalling reduces neuronal apoptosis, supports neuritogenesis and oligodendrocyte survival, which is important for myelin integrity. In neuron and glia cultures, MK-4/MK-7 is associated with enhanced neurotrophic support (particularly BDNF), improved synaptic plasticity, and long-term potentiation in the hippocampus, which is considered a molecular correlate of learning and memory.

The second important axis of K_2's neurobiological action is related to the control of neuroinflammation and oxidative stress. In a series of experimental studies, MK-4/MK-7 in micromolar concentrations inhibit NF-κB-dependent programmes in neurons and microglia, reducing the production of TNF-α, IL-1β, IL-6, iNOS and COX-2 expression, and the accumulation of oxidatively modified lipids. Some data indicate modification of NLRP3 inflammasome and PI3K/Akt, MAPK, and STAT/SOCS pathways, which may limit chronic "sterile" inflammation in the ageing brain. At the mitochondrial level, K_2 reduces the formation of reactive oxygen species and maintains $\Delta\Psi m$, thereby indirectly protecting neurons from programmed necrotic death and ferroptosis. More recent summaries highlight the anti-ferroptotic potential of MK-7 through increased GPX4 activity and reduced lipoperoxidation in models of neurodegeneration (Roumeliotis et al., 2025a).

The combination of these mechanisms translates into moderate but reproducible associations between vitamin K status and cognitive performance in humans. A systematic review found that lower dietary intake and lower serum K concentrations are associated with poorer memory and attention test scores in geriatric cohorts (Alisi et al., 2019). Higher dietary intake of vitamin K has been associated with better cognitive performance and less severe behavioural disturbances in hospitalised elderly patients (Chouet et al., 2015), as well as with less severe subjective memory complaints in elderly individuals who do not take vitamin K antagonists (Soutif-Veillon et al., 2016). Although most of these studies did not distinguish between K_1 and K_2, reviews focusing on K_2 emphasise that it is menaquinones with a longer half-life and better extrahepatic bioavailability that are more likely candidates for the role of neuroprotectors (Popescu & German, 2021).

There is also a body of data suggesting the possible neuroprotective potential of K_2 for the brain. A narrative review (Popescu & German, 2021) integrates the results of cell and animal models in which MK-4/MK-7 reduced β-amyloidogenesis, Aβ oligomer toxicity, mitochondrial dysfunction, and neuroinflammation, as well as improved cognition in models of Alzheimer's disease. Roumeliotis et al. (2025b) conclude that low K status (particularly K_2 deficiency) is associated with a risk profile – vascular stiffness, subclinical calcification, chronic systemic inflammation – that potentially accelerates neurodegeneration in older age. Additionally, data from small interventions with MK-7 in elderly patients with mild cognitive impairment suggest a possible slowing of hippocampal atrophy and moderate improvement in MoCA, but the findings need to be confirmed in larger randomised trials (Alisi et al., 2019; Popescu & German, 2021). From a gerontological perspective, vitamin K_2 can be considered a modifier of several "signs of ageing" in the brain (inflammaging, mitochondrial dysfunction, calcium homeostasis disorders, susceptibility to ferroptosis). At the same time, the level of evidence remains uneven: epidemiological data are consistent with the neuroprotective hypothesis, but long-term intervention studies with cognitive endpoints are limited.

Vitamin K_2 and reproductive function

Available data indicate the potential of K_2 as a modulating factor of reproductive homeostasis, while emphasizing the need for further research to clearly distinguish the effects of individual forms of menaquinones and their tissue specificity.

In the male reproductive system, attention is drawn to the possible link between vitamin K_2 levels and spermatogenesis quality. An association has been reported between K_2 content, the degree of

sperm DNA fragmentation, and apoptosis rates in the late stages of sperm maturation. In a biochemical context, this is consistent with the role of menaquinones in maintaining mitochondrial function and redox balance, which are critical for the energy supply and genomic stability of gametes (Ismael et al., 2025).

A separate area of research concerns the role of MK-7 in metabolic and endocrine disorders associated with polycystic ovary syndrome. In clinical observations, the addition of MK-7 was accompanied by changes in glycemic parameters, lipid profile, and levels of certain endocrine markers. In biochemical interpretation, these effects are associated with the influence of vitamin K_2 on insulin sensitivity, lipid metabolism, and signalling cascades that indirectly determine hormonal balance (Tarkesh et al., 2020; Gasieva et al., 2024).

At the level of the female reproductive system, it has been established that MK-4 is capable of influencing the transcriptional profile of endometrial cells. *In vitro* experiments have identified groups of MK-4 target genes associated with cell adhesion, lipid metabolism, ion transport, and intracellular signalling. Such changes in expression are considered to be the molecular basis for the involvement of vitamin K_2 in maintaining the functional plasticity of the endometrium and regulating processes related to implantation readiness (Bai et al., 2023).

Vitamin K_2 (menaquinones, primarily MK-4 and MK-7) is considered a factor involved in the regulation of reproductive processes at the cellular and tissue levels. Its action in the reproductive system is not related to the classic functions of haemostasis, but to the modulation of gene expression, energy metabolism, and redox homeostasis of the cells of the reproductive organs, which determines the functional state of the endometrium, gametes, and hormone-sensitive tissues (AlBlooshi, 2025).

The biochemical effect of K_2 on mitochondrial function is due to its ability to act as a mobile electron carrier in the respiratory chain, which allows it to partially compensate for defects in the electron transport chain and maintain ATP synthesis. In the reproductive system, menaquinones (particularly MK-4) are involved in the regulation of steroidogenesis, acting as cofactors in the pathways of testosterone synthesis in Leydig cells.

In summary, the effect of vitamin K_2 on reproductive function should be considered as a complex of cellular effects, including regulation of gene expression, modification of metabolic and redox processes, and indirect effects on hormone-sensitive tissues. The available data indicate the potential of K_2 as a modulating factor of reproductive homeostasis, while emphasizing the need for further research to clearly distinguish the effects of individual forms of menaquinones and their tissue specificity.

Digestive system, intestinal microbiota, and vitamin K_2

Vitamin K_2 (menaquinones) in the context of the digestive system should be considered as a metabolite at the intersection of two flows: food intake and microbial synthesis. The large intestine is characterized by the formation of a spectrum of menaquinone homologues, which is determined by the taxonomic composition of the community, the availability of substrates, and the energy regime of microorganisms (Bonaldo & Leroy, 2024). This means that the "K_2 profile" of the intestinal environment is an indicator of microbial metabolic activity, not just a reflection of diet.

The biochemical basis of microbial K_2 lies in its role as an electron carrier in bacterial electron transport chains. Therefore, the synthesis and turnover of menaquinones are sensitive to local redox conditions (oxygenation, availability of electron donors/acceptors) and are capable of changing along with the structure of the microbiota (Yan et al., 2023). In this context, menaquinones are not a "passive product" but a functional component of the microbial ecosystem"s energy system.

The interaction between vitamin K and the microbiota is bidirectional: on the one hand, the microbiota forms a pool and ratio of K_2 homologues, and on the other hand, dietary vitamin K and the food matrix can remodel microbial communities and, accordingly, their metabolic outputs. Metagenomic observations emphasize that dietary vitamin K intake is associated with changes in the composition of the microbiota, conceptualizing K-supply as a factor in intestinal ecosystem dynamics (Ellis et al., 2021).

It is important to avoid reducing the role of K_2 in the intestine to a purely protective one. Associations have been described between bacteria that produce long-chain menaquinone homologues and microbiota configurations correlated with the risks of colorectal carcinogenesis; This highlights the contextual dependence of effects on community composition and local epithelial signalling responses (Smajdor et al., 2023). Therefore, a correct biochemical interpretation must take into account not only the presence of K_2, but also "which" homolog dominates and in which ecosystem framework it is formed.

In summary, K_2 in the digestive system can be logically interpreted as a component of the "food matrix – microbiota – cellular processes" system, where the final biological effect is determined by a combination of dietary factors, microbial redox conditions, and the profile of menaquinone homologs (Ellis et al., 2021; Yan et al., 2023).

Vitamin K_2 and functional products

Functional products with vitamin K_2 should be positioned as technologically controlled systems in which menaquinones are formed or accumulated in the food matrix as a result of controlled microbial fermentation. The practical significance lies in the ability to "tune" not only the total K_2 content, but also the profile of homologues (e.g., the predominance of MK-7 or MK-8/MK-9) by selecting the producer and process parameters (Bonaldo & Leroy, 2024).

Biotechnological keys to obtaining K_2-enriched products include (I) selection of producer strains with predicted menaquinone productivity, (II) optimization of fermentation conditions (temperature, aeration/anaerobiosis, provision of isoprene chain precursors), (III) control of matrix properties that determine the stability and release of menaquinones. Review summaries emphasize that it is the technological parameters that can shift the ratio of homologues and thus influence the predicted bioactivity of the product (Bonaldo & Leroy, 2024).

Fermented traditional products serve as "natural models" of such controllability. Natto is characterized by the dominance of MK-7, associated with the fermentation activity of *Bacillus subtilis* (var. natto). In fermented milk matrices (certain types of cheese), the formation of menaquinones is associated with the activity of lactic acid and propionic acid bacteria; *Lactococcus lactis* and *Propionibacterium freudenreichii*, capable of forming long-chain homologues (more often MK-8/MK-9), are often considered technologically significant producers (Bonaldo & Leroy, 2024).

A promising direction is the use of starter cultures with a "predetermined" K_2 synthesis profile in beverages and fermented milk products (*Lactobacillus/Levilactobacillus* spp., *Leuconostoc* spp., *Enterococcus* spp.) subject to safety control and compliance with regulatory requirements. In these approaches, biochemical control of redox conditions and electron flows in the producer cell is essential, since menaquinones are endogenous components of bacterial electron transport chains (Yan et al., 2023).

A separate technological challenge is the ecosystem component: dietary K_2, coming with the product, interacts with the consumer"s microbiota and potentially affects its composition. Therefore, a correct scientific interpretation of functional products with K_2 should consider them in the "matrix-microbiota-metabolic responses" system and be accompanied by standardised analytical control of homologues in the finished product (Ellis et al., 2021).

Clinical aspects of use, safety, and doses of vitamin K_2

The clinical use of vitamin K_2 (mainly in the form of MK-7) in modern literature is considered through the prism of biochemical sufficiency for extrahepatic γ-carboxylation of vitamin K-dependent proteins and the stability of this effect during prolonged intake. On a practical level, this boils down to choosing the form (MK-4 vs. MK-7), the dosage range, and monitoring carboxylation markers as indicators of functional K status (Theuwissen et al., 2012).

The issue of safety primarily concerns interaction with the haemostasis system. Studies involving healthy individuals and postmeno-

pausal women have shown that low-dose MK-7 supplementation can enhance the carboxylation of extrahepatic proteins without clinically significant shifts in coagulation tests, which is consistent with the different "sensitivity" of hepatic and extrahepatic pathways to vitamin K availability (Theuwissen et al., 2012; Vlasschaert et al., 2020). At the same time, from a biochemical perspective, warfarin and other vitamin K antagonists remain direct inhibitors of the vitamin K regeneration cycle; therefore, K_2 supplementation in such cases should only be considered within controlled protocols and under laboratory monitoring.

The best-documented areas of application for MK-7 in food/nutraceutical logic are bone mineral homeostasis and markers of vascular calcification. Long-term observations in postmenopausal women have described improvements in parameters related to bone metabolism and osteocalcin carboxylation (Sato et al., 2020), as well as changes in vascular stiffness/elasticity parameters as integral characteristics of the vascular wall (Knapen et al., 2013). In the vascular context, the state of matrix Gla protein (MGP) as a calcification inhibitor is biochemically relevant, and its incomplete carboxylation is interpreted as a marker of increased calcification pressure (Hariri & Bell, 2021).

In populations with chronic kidney disease and hemodialysis patients, interest in K_2 is driven by the high prevalence of functional K-insufficiency and the accumulation of uncarboxylated fractions of calcification inhibitor proteins. Randomized protocols in such groups primarily evaluate biomarkers (dp-ucMGP and related indicators) and the rate of calcification progression, emphasizing the role of dosage and duration of intervention in achieving a measurable effect (Caluwé et al., 2014a).

Systematic reviews and meta-analyses indicate a generally favorable tolerability profile for K_2 at the doses studied, but also highlight the heterogeneity of designs, different forms of vitamin K, and differences in baseline K status that affect the comparability of results (Vlasschaert et al., 2020). Separately, it is pointed out that it is necessary to take into account the food matrix, which determines the absorption of lipophilic menaquinones, and genetic/metabolic factors of lipoprotein transport, which can modify the individual response (Zwakenberg et al., 2017).

Prospects for further research

Despite significant progress in understanding K_2 biology, research gaps primarily concern quantitative attribution of causality: for a number of associations between K status, carboxylation markers, and clinical phenotypes, protocols are needed that separate the contribution of K_2 from confounders of nutrition, inflammation, and lipid transport (Shea et al., 2021; Lyytinen & Linneberg, 2023). Additionally, the results of observational studies for high-risk populations need to be reconciled with data from interventional designs (Lyytinen & Linneberg, 2023).

Long-term randomised trials with clear stratification by baseline K status and menaquinone form (MK-4 vs MK-7), as well as unified endpoints for vascular calcification and stiffness, remain a key focus (Vlasschaert et al., 2020; Zhang et al., 2024). In the vascular context, comparative protocols that combine biomarkers (dp-ucMGP) with instrumental metrics of calcification and evaluate the role of MGP-dependent inhibition of calcification as a leading mechanism are appropriate (Vlasschaert et al., 2020; Hariri et al., 2021; Shea et al., 2021). Given the longer half-life and better bioavailability of MK-7 in extrahepatic tissues, this homologue is the most promising for the correction of systemic disorders that go beyond classical haemostasis.

At the level of molecular mechanisms, promising work is being done to clarify the non-carboxyl effects of K_2 (redox modulation, mitochondrial processes, nuclear receptors) in physiologically relevant models with controlled bioavailability and exposure (Kampmann et al., 2023). Within the framework of systemic biochemistry, it is also important to integrate data on K-dependent proteins with calcium-chelating and inflammatory mechanisms of the vascular wall, as these contours may explain different response phenotypes (Shea et al., 2021; Aaseth et al., 2023).

A separate block of further research concerns populations with mineral and lipid metabolism disorders (CKD/dialysis, metabolic syndrome), where not only clinical events are relevant, but also the biochemical trajectories of carboxylation, oxidative status, and inflammation markers (Aaseth et al., 2023; Roumeliotis et al., 2025b). Approaches to personalization based on "K-metabolotypes" (lipoprotein transport, vitamin K cycle genetics, microbiome contribution) with assessment of interactions in multifactorial models appear promising (Wu et al., 2025).

Finally, for consistency of review conclusions, systematic evidence maps are needed that distinguish the effects of K_2 form, dose, and delivery matrix, and also make transparent the limits of extrapolation from cellular models to the organism level (Kaźmierczak-Barańska et al., 2024; Zhang et al., 2024).

Conclusions

Vitamin K_2 is a biochemically important component of the regulation of vitamin K-dependent processes in extrahepatic tissues, primarily through the maintenance of VKDP γ-carboxylation and the functional state of Gla proteins. In a systemic measurement, this forms a link between K status and biomarkers of bone mineral and vascular homeostasis, as well as a number of cellular processes that depend on membrane and redox parameters.

Menaquinones with different side chain lengths (primarily MK-4 and MK-7) differ in their transport kinetics and tissue distribution; therefore, correct generalizations must be based on a clear distinction between chemical forms and control of dietary/technological factors of intake. From a biotechnological point of view, a promising approach is one that combines analytical standardization of K_2 homologues in products, assessment of bioavailability, and validation of functional carboxylation biomarkers.

The available data support the general view of a favorable tolerability profile of K_2 at the doses studied, but the evidence base needs to shift from fragmentary associations to reproducible cause-and-effect models with unified endpoints and stratification by baseline K status. In this logic, K_2 emerges as a nutrient modulator with biochemically defined targets rather than a universal "therapeutic" agent.

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