Menaquinone-7: From Fermentation Vessel to Vascular Evidence

Isomeric Purity, Microbial Biomanufacturing, Vitamin K–Dependent Carboxylation, Clinical Trials and European Food Law

INTABIOTECH KNOWLEDGE CENTER · SCIENTIFIC & REGULATORY REVIEW 008 · NOVEMBER 2026

José M. López, BSc, MD, PhD, LLD (C)

Research Director · INTABIOTECH

ORCID: **0009-0006-9238-0080**

Critical interdisciplinary review · Molecular biochemistry · Food biotechnology · Human clinical evidence · Industrial development · European regulatory science

Abstract

Menaquinone-7 (MK-7), a long-chain member of the vitamin K_2 family, has become a technically consequential ingredient because its biological function can be investigated through precisely identified molecules, fermentation-derived manufacturing routes and measurable vitamin K–dependent proteins. Nevertheless, its translation from bacterial metabolism to finished food and clinical evidence is more intricate than the commercial expression "vitamin K_2" implies. This interdisciplinary critical review examines MK-7 molecular configuration, quinone-dependent biosynthesis, production by *Bacillus* fermentation, co-production with extracellular enzymes, purification, chromatographic characterisation, delivery-system engineering, exposure assessment and European food law. Two particularly significant 2026 randomized studies inform the clinical analysis. The VitaK-CAC trial, using 360 µg/day MK-7 for two years in patients with symptomatic coronary artery disease and moderate baseline coronary calcification, reported a statistically significant difference in coronary calcium progression. The DANCODE trial, enrolling participants with severe baseline calcification, likewise reported attenuation of calcium-score progression using 720 µg/day MK-7 combined with 25 µg/day vitamin D_3. These findings warrant serious investigation, while differing treatment compositions, baseline disease, imaging endpoints and the absence of established cardiovascular-event reduction prevent their conversion into a generic therapeutic proposition. The review also evaluates the distinction between changes in dephosphorylated-uncarboxylated matrix Gla protein and demonstrated clinical outcomes and analyses the EU Union-list specifications for menaquinone-7, food-supplement and fortification frameworks, permitted vitamin K claims and the particular significance of vitamin K antagonists. Finally, it proposes an industrial evidence programme that integrates production-strain qualification, all-trans MK-7 identity, batch reproducibility, finished-food stability, biologically meaningful exposure, lawful communication and scale-up economics. The practical opportunity is to develop accurately specified micronutrient ingredients whose performance is reproducible from fermentation vessel to saleable serving—not to infer clinical effectiveness from a nominal vitamin percentage.

Keywords: *menaquinone-7; vitamin K_2; all-trans MK-7; natto; Bacillus subtilis; microbial fermentation; gamma-carboxylation; matrix Gla protein; osteocalcin; coronary artery calcification; VitaK-CAC; DANCODE; bioavailability; anticoagulants; EU novel foods; nutrition and health claims; analytical quality.*

1. An established vitamin acquires an unfamiliar industrial identity

Vitamin K has long been recognised as essential to haemostasis. What has changed is the ability to manufacture a specific vitamin K homologues with tightly specified chemical identities and to examine their contribution to extrahepatic vitamin K–dependent protein biology. This change is more important than the appearance of another vitamin in a supplement catalogue. It allows an ingredient supplier to ask whether a defined molecular form, produced by an auditable process and incorporated into a particular matrix, produces a measurable exposure and a reproducible response. It also forces a discipline frequently absent from discussions of micronutrients: a nutritional category, a molecule and a commercial preparation are three different objects.

The industrial word "K_2" covers several menaquinones, conventionally designated MK-*n* according to the number of isoprene units in their side chain. Natto is particularly associated with MK-7, while other fermented and animal-derived foods may contain different menaquinone distributions. A result obtained with MK-7 cannot be reassigned automatically to MK-4 or MK-9, and the reverse is equally problematic. Even within MK-7, geometric isomers, residual related menaquinones and delivery vehicles may distinguish preparations whose labels display an identical nominal vitamin amount.

The second change is clinical. During 2026, two controlled studies reported favourable coronary-calcium imaging findings in selected populations receiving MK-7 alone or in combination with vitamin D_3 (Vossen et al., 2026; DANCODE investigators, 2026). Their results deserve attention precisely because previous studies in haemodialysis and valvular disease had not consistently translated changes in vitamin K biomarkers into anatomical benefit. Taken together, this is an evolving experimental field, neither a completed cardiovascular treatment evidence base nor merely a biochemical conjecture.

This review uses literature and European instruments available through 19 November 2026. It is a critical narrative synthesis, not a registered systematic review, primary clinical trial or regulatory authorisation opinion.

2. Molecular architecture: menaquinone identity extends beyond seven isoprenoid units

Phylloquinone (vitamin K_1) and menaquinones (vitamin K_2) share a 2-methyl-1,4-naphthoquinone core but differ in the hydrophobic side chain. MK-7 has seven isoprenoid units and an approximate molecular formula $C_{46}H_{64}O_2$ and molar mass of 649 g/mol. This architecture contributes to its pronounced lipophilicity, interaction with lipid carriers and plasma transport characteristics. Those features influence formulation and pharmacokinetics but should not be treated as a direct numerical measure of superior health outcomes.

The configuration of the isoprenoid double bonds matters. Commercial MK-7 is commonly discussed in terms of an all-trans configuration, whereas synthetic routes may also produce cis geometric isomers. A total MK-7 assay that cannot resolve geometrical species may misdescribe the quantity of the intended active configuration. In the EU Union-list specification for **synthetically produced** MK-7, the authorised ingredient is defined with explicit requirements including a minimum all-trans content and limits for cis-isomer and other impurities. Those numerical specifications must not simply be projected onto the separate microbiologically produced material without checking its own legally applicable entry.

Chemical purity, therefore, has at least three levels. The first is correct assignment of the menaquinone homologue. The second is geometrical identity within MK-7. The third is the composition of the supplied grade: oil suspension, powder, carrier, antioxidant, residual processing components and related metabolites. Product development can fail at any level. An ingredient may satisfy an assay for total menaquinone but contain a carrier unsuited to a clear beverage; another may meet a chromatographic identity test at manufacture but undergo measurable loss in a transparent package exposed to light.

The term “natural” does not resolve these questions. Fermented MK-7 is obtained through biology but requires cultivation, extraction and purification. Synthetic material may achieve an analytically defined stereochemical profile under a different manufacturing route. The relevant scientific and legal questions are compositional equivalence, process qualification, safety, intended use and demonstrated performance, rather than an unexamined hierarchy of origin narratives.

3. The vitamin K cycle connects nutrition to protein carboxylation

The principal mechanistic rationale begins with the vitamin K cycle. Vitamin K hydroquinone serves as a cofactor for gamma-glutamyl carboxylase, which converts selected glutamate residues in vitamin K–dependent proteins into gamma-carboxyglutamate (Gla) residues. Carboxylation permits concrete proteins to bind calcium or fulfil their biological function. Vitamin K is oxidised during the reaction and then recycled through enzymatic pathways involving vitamin K epoxide reductase and other reductive systems. Vitamin K antagonists, including warfarin and acenocoumarol, alter this cycle and therefore its effects on coagulation-related proteins.

At least three protein systems are relevant to the ingredient discussion. Hepatic coagulation factors establish the indispensable classical function of vitamin K. Osteocalcin, a bone-associated Gla protein, is often used to investigate vitamin K–dependent carboxylation in skeletal physiology. Matrix Gla protein (MGP) is a locally produced inhibitor of ectopic mineralisation, and its activation has motivated research on vascular calcification. The presence of a biochemical mechanism does not mean that these proteins respond identically to a given intake, nor that a marker of one tissue predicts the outcome of another.

Dephosphorylated-uncarboxylated MGP (dp-ucMGP) is commonly measured as an indicator of functionally insufficient MGP maturation and vitamin K status in a vascular context. MK-7 supplementation can lower circulating dp-ucMGP in controlled studies. This is real mechanistic engagement; it is not itself a direct image of arterial calcification. To establish an anatomical effect requires appropriate imaging studies; to establish reduction in clinical events requires still another class of trial with sufficient participants, duration and event ascertainment.

The distinction matters for both clinical interpretation and industrial research. Measuring plasma MK-7 demonstrates systemic exposure. Measuring dp-ucMGP contributes evidence of pathway engagement. Measuring coronary artery calcium with computed tomography assesses a structural imaging outcome. Counting myocardial infarctions, strokes, admissions and deaths assesses patient-relevant events. Each measurement occupies a different evidentiary level, with its own biological meaning, measurement error and appropriate study design. An integrated programme should preserve the sequence rather than collapse it into the phrase “cardiovascular protection.”

4. Engineering MK-7 by fermentation

Natto fermentation offers a historically established context for MK-7 production, but industrial manufacture is not simply a scaled-up serving of fermented soybeans. In a controlled platform, an authenticated production strain of *Bacillus subtilis* group organisms is supplied with appropriate carbon, nitrogen, mineral and oxygen conditions. Metabolic flux through the bacterial quinone pathway supports menaquinone biosynthesis, while cell growth, sporulation, extracellular polymer formation and other metabolic outputs compete for resources and influence broth behaviour.

The economics of this process depend on saleable MK-7, not merely cell density or concentration of a target signal in a laboratory assay. Relevant attributes include strain stability across passages, fermentation time, oxygen-transfer capacity, carbon-source utilisation, foam, broth viscosity, contamination control, extraction yield, purification loss and stereochemical integrity. Feeding more substrates can increase biomass while decreasing product yield per unit substrate if another metabolic pathway becomes limiting. A nominal titre reported for a small shake flask should not be used as the sole basis for a commercial production cost model.

Fermentation engineering must also separate synthesis from recovery. After production, the matrix may contain viable organisms or spores, extracellular proteins, peptides, poly-gamma-glutamic acid, substrate residues and other microbial metabolites. The intended vitamin grade may require cell separation, cell disruption or extraction, controlled concentration, filtration, purification, solvent management where relevant, oxidation protection and final dilution into a commercial carrier. Different downstream routes can produce similar measured MK-7 levels yet substantially different impurity profiles and storage behaviour. A supplier dossier should connect every critical operation to a validated final attribute.

Recent fermentation research has explored MK-7 process optimisation and systems that also produce nattokinase, an extracellular serine protease. Such studies reveal that microbial manufacturing can yield several commercially interesting fractions from the same organism. They do not mean that each fraction shares the vitamin's regulatory identity, safety evaluation or clinical evidence. The producer must separately qualify material intended for use as a vitamin source and any recovered enzyme or other co-product.

5. Co-production is a metabolic design problem, not proof of equivalent products

A 2026 original investigation of *Bacillus subtilis* MM26 reported co-production of MK-7 and nattokinase, with respective reported maxima at different fermentation times: approximately 155.1 ± 1.24 U/mL for nattokinase at 72 hours and 67 ± 0.6 mg/L for MK-7 at 120 hours (Maneesha and Subathra Devi, 2026). The different kinetics are more instructive than the simple fact of co-production. An operation optimised for early extracellular protease recovery may not maximise later intracellular or cell-associated quinone yield.

A 2026 interdisciplinary review of *B. subtilis* natto co-production highlighted the biological contrast between a secreted enzyme and a membrane-associated quinone product. Process-control variables may favour one pathway over another. Consequently, fermentation should be designed around a defined product hierarchy or a deliberately engineered cascade. If two products are commercially valuable, harvesting time, pH, aeration and downstream fractionation may be optimised jointly, but only against measured yields and validated quality specifications (Co-Production of Nattokinase and Menaquinone-7, 2026).

The distinction has direct regulatory significance. MK-7, when supplied as vitamin K_2, belongs to a specific novel-food and fortification framework. A protease obtained from the same fermentation has its own identity, potential food-enzyme or other regulatory questions and separate evidence requirements. The lawful status of one does not confer blanket approval on another. A multi-product operation can be efficient while remaining legally and technically multi-dossier.

An industrially credible study would therefore track MK-7 and protease activity across the fermentation cycle, assess their distribution between solid and liquid fractions, calculate total mass balance and measure whether recovery of one decrease purity or stability of the other. That approach converts a promising production concept into a testable engineering proposition and identifies when a seemingly attractive integrated process is inferior to purpose-specific manufacture.

6. Four independent questions define an acceptable MK-7 ingredient

For an ingredient to be industrially acceptable, its chemical identity, lawful manufacture, finished-matrix performance and physiological proposition all need separate evidence. These are related but cannot be substituted for one another. A clean chromatogram confirms neither bioavailability nor legal permission in a particular beverage. A favourable human trial does not validate a supplier with a different isomer profile. And the appearance of vitamin K in a European health-claims regulation does not remove the obligation to meet novel-food specifications where relevant.

Table 1. The principal identities and decisions in an MK-7 development programme

Evidence level	Principal variables	Appropriate measurements	Decision that the evidence can support
Molecular identity	MK homologue, geometric isomers, all-trans content	Isomer-resolving chromatography, validated standards	Is the named active composition actually present?
Manufacturing identity	Production strain, fermentation or synthetic route, impurities	Strain authentication, process records, release and purity data	Does supply match the authorised ingredient specification?
Formulation identity	Carrier, dispersion, protection from oxygen and light	Recovery, homogeneity, shelf-life and compatibility studies	Is the intended amount present throughout product life?
Biological exposure	Dose, absorption and transport	Human plasma MK-7 where scientifically warranted	Does the preparation provide systemic exposure?
Functional pathway	Vitamin K–dependent protein carboxylation	dp-ucMGP and selected bone/coagulation biomarkers	Is the investigated pathway engaged?
Clinical outcome	Defined population, disease stage, treatment, endpoint	Controlled trials, appropriate imaging or hard events	What health effect has actually been demonstrated?

Evidence level	Principal variables	Appropriate measurements	Decision that the evidence can support
EU communication	Exact food, quantity, authorised statement	Union-list and health-claims legal review	What may lawfully be stated to consumers?

This table is an evidence map, not a declaration that every proposed product or use is authorised.

7. All-trans purity, potency and analytical release

Quantitative analysis of a lipophilic vitamin requires particular care. High-performance liquid chromatography is a common approach; validated separation and appropriate detectors, potentially supplemented by mass spectrometry or orthogonal structural analysis, can establish the MK-7 homologue and relevant geometric isomers. A producer cannot demonstrate all-trans specification merely by reporting a general vitamin K_2 peak if the method fails to resolve cis species. Calibration purity, response factors and the basis on which dilution or assay correction is made should be recorded.

Commercial products can contain MK-7 as concentrated powder, diluted powder, oil solution, beadlet, emulsion or other presentation. A statement such as “0.2% MK-7” is incomplete until it specifies whether the percentage means all-trans MK-7, total MK-7, active vitamin after a stated assay adjustment or nominal addition. The certificate of analysis should identify the actual assay method, reference standard, tolerances, carrier and storage specification. Results obtained after extraction from an oil suspension may not be directly interchangeable with those from a carbohydrate-rich powder without suitable recovery validation.

Contaminants and process-related residues must be assessed according to the source and manufacturing route. Fermentation preparations warrant suitable microbial testing, production-strain control and, as appropriate, evaluation of process residues. Synthetic material raises its own impurity-profile questions. The appropriate requirements are those imposed by the specific applicable legal specification and validated hazard assessment; “food grade” is a commercial expression, not a substitute for this analysis.

Stability validation should measure the intended isomer rather than total colour or a generic vitamin signal. MK-7 is sensitive to formulation environment and potentially to photochemical or oxidative stress. Finished-food testing should investigate storage temperature, oxygen exposure, packaging light transmission, moisture, carrier interactions and changes in geometric profile where analytically relevant. Overages may be considered only within an accurate, safe and lawful formulation rationale; they cannot conceal an inherently unstable ingredient system.

8. Food matrices alter the delivered vitamin

MK-7 is lipophilic, and the vehicle in which it is presented may affect dispersion, gastrointestinal handling and systemic exposure. Natto, an oil-based capsule, an emulsified beverage and a dry premix impose different physical environments. In lipid-rich food, the compound encounters co-ingested fat, lipid digestion and micellar solubilisation. In low-fat aqueous systems, formulation design must create and preserve a suitable dispersed or carrier-associated state. Appearance in a visually clear solution is not proof of molecular solubility or human bioavailability.

A 2025 randomized human study evaluated a nano-encapsulated preparation derived from natto extract and reported higher plasma MK-7 exposure under selected comparison conditions (Cong et al., 2025). Such studies demonstrate the utility of comparing delivery systems with measured pharmacokinetic endpoints. They do not by themselves establish that every nano-formulation is safe, legally equivalent or physiologically superior in the long term. Product developers should distinguish relative plasma exposure from protein carboxylation, and both from hard clinical benefit.

Food processing creates additional variables. Thermal treatment may affect the supporting carrier and surrounding matrix even when the vitamin survives adequately. Fermented dairy can alter emulsion structure and acidity; cocoa and confectionery introduce fat-phase partitioning, oxidative chemistry and extended shelf-life demands; protein bars create challenges of blending uniformity and local migration. The appropriate study compares the finished product before and after processing and across realistic storage, not only the incoming vitamin concentration in a supplier laboratory.

A useful ingredient dossier would state measurable performance parameters for each target use: assay recovery after mixing, permitted dose and serving size, between-unit homogeneity, oxidative and photochemical stability, sensory neutrality, packaging compatibility and batch variability. These measurements are not interchangeable with human efficacy, but they establish whether a finished food can credibly reproduce the investigated exposure.

9. Clinical evidence before 2026: a mechanism seeking reliable anatomical endpoints

The history of vitamin K_2 vascular research explains why the 2026 trials attract attention. Observational associations and mechanistic studies established an appealing rationale: if carboxylated MGP inhibits ectopic mineralisation, improved

vitamin K status might influence calcium deposition in arteries or valves. Supplementation studies frequently demonstrated lower dp-ucMGP, indicating engagement of vitamin K–dependent carboxylation. Yet controlled trials had not produced a uniformly favourable effect on imaging endpoints in chronic kidney disease, haemodialysis and other populations (Trevasc-HDK investigators, 2023; Vitamin K and vascular calcification, 2026).

The AVADEC trial and related coronary analyses studied combined vitamin K_2 and vitamin D in older men with aortic-valve calcification. The principal valve-related findings were not a general demonstration of prevention, although coronary subgroup observations contributed hypotheses for further research. Such distinctions are critical: a valve outcome, a coronary calcium score and an arterial-stiffness measure should not be rhetorically merged into a single “calcification” effect. Furthermore, vitamin D is a co-intervention capable of influencing calcium physiology and complicating the attribution of any difference solely to MK-7.

For bone health, trials have examined undercarboxylated osteocalcin, biochemical markers, bone mineral density and fracture-related endpoints. Their consistency varies with population, baseline status, dose and duration. A reduction in undercarboxylated osteocalcin demonstrates a plausible biochemical effect; it does not independently establish lower fracture rates. Importantly, the European Union has authorised a general vitamin K statement concerning maintenance of normal bones under defined conditions, but this legal authorisation is not a product-specific endorsement of a novel MK-7 delivery technology or a broad claim to reverse osteoporosis.

What was missing across much of the historical literature was a direct and consistent connection among analytical intake, biomarker change, structural imaging and clinically meaningful outcomes. The question for a new generation of trials is therefore not whether MK-7 is biologically active. That is the least controversial part of the chain. The harder question concerns which populations and disease stages might translate pathway engagement into an anatomical effect that ultimately matters to patients.

10. The 2026 coronary trials: two positive imaging signals, different interventions

In the Dutch VitaK-CAC randomized study reported by Vossen and colleagues, 180 participants with symptomatic coronary artery disease and coronary artery calcium (CAC) scores between 50 and 400 Agatston units were assigned to 360 µg/day MK-7 or placebo for two years. The investigators measured CAC and calcium mass on serial computed tomography. At two years, median CAC scores in the reported groups had increased from 145 to 214 Agatston units with placebo and from 135 to 184 with MK-7. The between-group difference in longitudinal progression was statistically significant (P = .02), with a similar direction for calcium mass. Plasma MK-7 rose significantly, supporting exposure fidelity. The result is a serious controlled indication of slower coronary calcification under the specific conditions studied (Vossen et al., 2026).

The effect is neither a universal treatment recommendation nor a demonstration that reducing calcium score progression necessarily reduces clinical events. Coronary calcium may increase as plaque biology changes; calcification and plaque stability are not simply opposing quantities. The trial did not establish reductions in infarction, stroke or mortality. Moreover, the study population excluded several important clinical groups, including individuals using vitamin K antagonists, and the results cannot be assumed to apply across all cardiovascular states. Those boundaries refine the finding; they do not erase it.

The Danish multicentre DANCODE trial presented a second positive result in 2026. It randomised approximately 400 participants with more severe baseline coronary calcification (CAC at least 400 Agatston units) to vitamin K_2 720 µg/day **plus vitamin D_3 25 µg/day**, or placebo, for 24 months. Reported mean CAC progression was approximately 196 Agatston units in the combined-supplement group and 248 in the placebo group, corresponding to a between-group difference of about −52 units (95% CI approximately −79 to −24). This trial is important because it tested a prespecified imaging endpoint in a population with substantial baseline disease (DANCODE investigators, 2026).

Its design also imposes a distinct interpretive constraint. DANCODE tested a *combination*, not isolated MK-7. It cannot identify how much of the difference arose from MK-7, vitamin D_3, their interaction or other aspects of the intervention. The dose of MK-7 was twice that used in VitaK-CAC, but neither population nor treatment was otherwise identical; comparing the effect sizes as a simple dose-response experiment would be scientifically unjustified. The trials nonetheless converge on a question worthy of future testing: whether certain coronary-disease phenotypes show a reproducible imaging response to vitamin K–based supplementation.

Table 2. Interpretation of the major controlled cardiovascular evidence

Trial / context	Exposure and population	Reported result	What remains unresolved
VitaK-CAC, 2026	MK-7 360 µg/day versus placebo; 180 randomised; symptomatic coronary disease; baseline CAC 50–400 AU; 2 years	Significantly slower CAC progression (P = .02); corresponding calcium-mass signal	Effects on cardiovascular events, broader populations and long-term clinical outcomes
DANCODE, 2026	MK-7 720 µg/day + vitamin D_3 25 µg/day versus placebo; 400 randomised; CAC ≥400 AU; 2 years	Less CAC progression; difference approximately −52 AU	Independent contribution of MK-7, event reduction and transfer to other disease stages
AVADEC and prior coronary analyses	MK-7 + vitamin D_3; older men with valvular calcification	Main valve findings were neutral; coronary subgroup findings generated hypotheses	Validity beyond selected subgroups and combined-intervention setting
Trevasc-HDK, haemodialysis	MK-7 versus control, approximately 18 months	dp-ucMGP decreased without consistent imaging or cardiovascular-event benefit	Whether renal disease changes biology or responsiveness

The numbers describe reported trials. CAC is an imaging surrogate; none of the studies proves a marketed food prevents cardiovascular disease.

11. Reading a calcium score without confusing anatomy with prognosis

Coronary artery calcium is not an interchangeable synonym for cardiovascular risk reduction. The Agatston score is a computed-tomography-derived measurement reflecting the area and radiological density of coronary calcified lesions. It predicts risk at a population level and provides a quantitative way to follow calcification; however, the relation between its change over time and plaque biology is more complicated than a model in which every additional calcified unit represents an equal increment of danger. Calcification may accompany plaque maturation or alterations in composition. Several contemporary cardiology analyses therefore warn against treating calcium-score progression alone as a fully validated surrogate for fewer myocardial infarctions.

This difficulty is especially relevant when interpreting a nutrient whose proposed mechanism involves a natural inhibitor of ectopic calcification. The expected mechanistic direction is clear enough to justify intervention trials. Yet the clinical objective must still be defined: is the study intended to change biochemical carboxylation, calcium deposition, plaque morphology, plaque stability or rates of clinical events? Each objective requires distinct measurement and statistical assumptions. A trial can answer one question well without answering all of them.

The positive 2026 imaging findings are stronger than an isolated cell-culture result and deserve to be reported as such. They also differ from a regulatory health-claim assessment, where evidence must support a sufficiently established cause-and-effect relationship for the intended statement and conditions of use. A supplier who replaces the two-year imaging endpoints with the consumer phrase “prevents atherosclerosis” would introduce a new scientific proposition that the underlying trials did not measure.

Future studies would benefit from predefined cardiovascular events, more extensive plaque characterisation, adequate population diversity, stratification by baseline calcification and vitamin K status, and careful control of concomitant statins, antithrombotic treatment and vitamin D exposure. Because calcification changes slowly, study length and adherence are critical. Whether the new 2026 signals survive independent confirmation will depend as much on trial architecture as on an additional increase in MK-7 dose.

12. Biomarkers are useful precisely because they are not the final endpoint

A coherent MK-7 development dossier should retain biomarkers while assigning them an appropriate role. Plasma MK-7 can help verify that the intervention increases exposure. Undercarboxylated osteocalcin may indicate a response in the bone-associated protein system. Dp-ucMGP informs the vascular carboxylation hypothesis. None should be discarded simply because it is not a clinical event; doing so would remove information required to explain variation between trials. The problem arises only when a biochemical response is treated as proof of an anatomical or health outcome.

The distinction is especially evident in kidney disease. Several studies report substantial changes in dp-ucMGP without a commensurate improvement in calcification progression. Chronic kidney disease presents disturbances in mineral metabolism, inflammation, phosphate regulation and vascular injury that may not be fully corrected by supplying one cofactor. This is a scientifically plausible explanation for discrepancies, but each individual pathway remains a hypothesis to be evaluated rather than an established account of why a particular trial failed (Trevasc-HDK, 2023; Clinical Kidney Journal, 2026).

There is also a measurement problem. Circulating concentrations reflect production, modification, clearance and distribution, potentially influenced by renal function and other patient characteristics. Even a highly precise biomarker assay is not necessarily a perfect measure of the functional status of an individual vessel wall. This difference should be made explicit in study protocols and in the interpretation of response heterogeneity.

For food-ingredient development, the appropriate path is a staged programme. Physicochemical qualification comes first. Where human exposure is relevant, pharmacokinetic or biomarker studies may then establish whether a particular delivery system reproduces the intended biological dose. Only when a meaningful outcome hypothesis remains should expensive patient-level trials be considered. A low-cost biomarker study may be a useful decision gate, but it cannot replace the clinical investigation needed for an ambitious claim.

13. Clinical safety and the anticoagulation interface

Vitamin K is not merely another botanical antioxidant; it is a functional nutrient within a pharmacologically targetable pathway. Vitamin K antagonists inhibit recycling of active vitamin K and reduce the functional activity of several clotting proteins. Increasing vitamin K intake can therefore alter anticoagulant response and international normalised ratio (INR) control in people using medicines such as warfarin or acenocoumarol. A fortified food or supplement that changes habitual vitamin K intake may be relevant even where its dose seems unremarkable to a consumer not receiving anticoagulants.

The responsible interpretation is not that all consumers should avoid dietary vitamin K, nor that patients should make unmonitored changes. Clinical guidance stresses the importance of a consistent intake and professional review before starting vitamin K-containing supplements during treatment with vitamin K antagonists (NIH ODS, 2026; NHS, 2024). The precise implications depend on the drug, regimen and clinical monitoring. Direct oral anticoagulants have a different primary mode of action; they should not be conflated with vitamin K antagonists, although clinical decisions about supplements remain individual.

For manufacturers, this interface should influence target-population selection, product communication and foreseeable exposure assessment. A consumer-facing claim that the ingredient “improves blood circulation” could be especially problematic if it suggested a pharmacological effect or encouraged anticoagulated patients to self-medicate. Similarly, a product labelled only with an obscure ingredient grade may fail to communicate its vitamin K content clearly enough to support informed use, even if it otherwise satisfies formal composition rules.

Safety qualification must additionally consider source identity, impurity specifications, long-term intake, co-formulated vitamins, consumer age and product category. It is inaccurate to treat the absence of a generally established upper tolerable intake level for vitamin K as proof that all concentrated MK-7 products are appropriate for all consumers. Toxicological reference systems authorised novel-food conditions and clinically relevant interactions answer different questions. A safety dossier should handle each through its own evidence.

14. The European legal identity of MK-7

The European legal position is more precise than a generic statement that vitamin K_2 is an authorised vitamin. Commission Decision 2009/345/EC originally authorised vitamin K_2 obtained from *Bacillus subtilis* natto as a novel food ingredient under the predecessor novel-food system. The current framework is Regulation (EU) 2015/2283, with the Union list established by Commission Implementing Regulation (EU) 2017/2470, as amended. The Union-list entry for vitamin K_2 (menaquinone) encompasses defined manufacturing routes and specifications, including synthetic and microbiological material, and sets conditions of use linked to other vitamin legislation.

Crucially, the Union list is not a blanket commercial approval for every menaquinone-containing fermentation extract. The current entry identifies specific microbiological sources and a defined synthetic MK-7 composition. A material made using another organism, a different process or a substantially changed composition must be assessed against the actual authorised description and the rules on novel food identity. The presence of MK-7 in natto as a traditional food is relevant historical context but does not prove that a highly purified preparation made by an unrelated industrial process has the same regulatory status.

The synthetic MK-7 specification is particularly concrete: according to the Union list, it includes all-trans MK-7 in a defined quantitative range, a maximum cis-isomer content of 6.0% and a maximum of 2.0% other impurities, among other requirements. These are not universal analytical tolerances for all vitamin K_2 products or all fermentation-derived grades. The exact specification row must be applied to the actual material. The microbiological route has its own specification and source descriptions; matching a nominal assay percentage is insufficient if production identity differs.

Authorised use also interacts with Directive 2002/46/EC on food supplements, Regulation (EC) No 1925/2006 on addition of vitamins and minerals to foods, and Regulation (EU) No 609/2013 where foods intended for specified groups are

involved. Annexes on permitted vitamin and mineral substances, category restrictions, quality rules and national implementation requirements require product-specific verification. A novel-food entry and a listed vitamin source address related but distinct aspects of legality. Neither excuses the other.

This legal architecture has significant procurement consequences. Two offers labelled “MK-7 2,000 ppm” may differ in isomeric specification, legal route, production source and permitted application. The cheapest analytical price per gram is immaterial if the ingredient cannot be incorporated lawfully into the client's planned food. A serious purchasing review therefore begins with the exact identity and intended use, not with a negotiation over nominal potency.

15. Authorised vitamin K claims and the boundaries of cardiovascular messaging

European Regulation (EC) No 1924/2006 controls nutrition and health claims. Commission Regulation (EU) No 432/2012 lists two relevant authorised general-function statements: **“Vitamin K contributes to normal blood clotting”** and **“Vitamin K contributes to the maintenance of normal bones.”** Their use is conditioned on the food being at least a source of vitamin K under the relevant nutrition-claim requirements. These statements are not equivalent to a statement that MK-7 prevents coronary calcification, treats osteoporosis, reduces fracture incidence or lowers cardiovascular mortality.

The nutrition-labelling reference value for vitamin K under Regulation (EU) No 1169/2011 is 75 µg. That number must be distinguished from EFSA's 2017 adult adequate intake of 70 µg/day, which serves a different scientific purpose. Under Annex XIII, general significance criteria include 15% of the reference value per 100 g for foods, 7.5% per 100 mL for beverages, or 15% per portion where the package contains a single portion. The resulting arithmetic is 11.25 µg per 100 g or 5.625 µg per 100 mL for the relevant cases. The formula and precise label presentation must be checked against the applicable rules and the actual product format; these thresholds do not establish safety or permission to use an otherwise non-compliant MK-7 ingredient.

A hypothetical beverage supplying 75 µg vitamin K per stated serving might be nutritionally meaningful, but a label cannot automatically adopt a broad vascular claim because it contains the vitamin or because DANCODE found a difference in an imaging endpoint. The claim must be an authorised claim in the appropriate category, and its exact conditions must be satisfied. A statement using “K_2” in place of “vitamin K” may require scrutiny to ensure that the substance is appropriately identified and the message retains the authorised meaning.

Regulation (EU) No 1169/2011 also requires food information not to mislead consumers. Product description, vitamin amount, serving size, ingredients and any special consumer information should be mutually consistent. Clinical-trial doses of 360 or 720 µg/day cannot be treated as mandatory, optimal or universally suitable commercial doses merely because they appeared in controlled studies. Neither dose determines the health-claim authorisation, which follows a separate legal test.

Table 3. European regulatory questions for MK-7 materials and finished foods

Question	Main EU instrument	Required determination	Invalid assumption
Is the supplied MK-7 a lawful novel food?	Regulation (EU) 2015/2283; Union list 2017/2470	Source, manufacturing process, stereochemical and purity specification	“Every fermentation-derived MK-7 is the same approved ingredient”
May this form be used for vitamin addition?	Directive 2002/46/EC; Regulation (EC) 1925/2006	Permitted source, product type, applicable rules and dose	“Novel-food listing alone permits every food application”
What may the nutrient declaration show?	Regulation (EU) 1169/2011, Annex XIII	Measured vitamin content and 75 µg reference value	“Fermentation input determines the finished label value”
May the food claim bone or coagulation function?	Regulations (EC) 1924/2006 and (EU) 432/2012	At least a source of vitamin K; compliant wording and conditions	“Any measurable MK-7 amount permits the health claim”
May the food claim cardiovascular treatment?	EU health-claims system; general food-information rules	Specific relevant authorisation, if any, and lawful message	“Positive CAC imaging trials authorise prevention claims”
Is communication suitable for anticoagulated consumers?	General food safety and information; relevant national context	Foreseeable interaction risk and accurate presentation	“Vitamin ingredients cannot affect prescribed medication”
Does the exact finished food remain compliant?	Regulation (EC) 178/2002; Regulation (EC) 852/2004 and category-specific law	Batch quality, hygiene, composition, traceability and exposure	“A supplier certificate completes the finished-food assessment”

16. Three application environments with different technical decisions

16.1. Oil-based food supplements. An oil suspension can offer a relatively direct route to a dose of lipophilic MK-7, but it does not dispense with assay, homogeneity, fill-weight and oxidative stability requirements. The producer should verify the

concentration of all-trans MK-7 in finished units rather than rely on theoretical premix addition. Oil identity, packaging, oxygen exposure and storage duration determine whether the delivered amount remains within specification. If vitamin D_3 is added, that creates a combined preparation whose nutrient claims, safety evaluation and potential evidence positioning require independent consideration; the formulation cannot be described as clinically equivalent to the DANCODE intervention without comparative evidence.

16.2. Enriched dairy or fermented dairy-type foods. Milk fat or other lipids may provide a suitable physical environment for MK-7, but processing and fermentation can redistribute or transform the vitamin-bearing phase. Experimental validation should include homogenisation, pasteurisation, fermentation kinetics, container filling and shelf-life measurement. If a production culture is claimed to generate MK-7 *in situ*, its actual menaquinone output, strain identity and legal status must be demonstrated. A culture's general ability to produce quinones does not establish that the finished yogurt or cultured beverage contains a reproducible, label-worthy MK-7 dose.

16.3. Protein beverages, bars and composite foods. Low-fat protein drinks present an emulsion or carrier challenge; certain protein ingredients and minerals can alter interfacial behaviour, haze and stability. Dry powders and bars present other risks, including micro-ingredient segregation, moisture migration, mixing losses and exposure to processing heat. In confectionery, incorporation into a lipid-continuous filling may be easier than into an aqueous beverage, but cocoa and fat systems impose their own oxidative and sensory controls. A successful food-system design must specify the intended dose at consumption, not simply successful addition at manufacture.

Across the three environments, the basic experimental principle is the same: the ingredient's chemical identity must survive manufacturing and storage, while the matrix remains safe and commercially acceptable. The optimisation variables, however, are different. An industrial supplier should not market one generalised MK-7 stability figure as if it described all product formats.

17. A worked industrial design: an MK-7-enriched cultured beverage

Consider a hypothetical manufacturer developing a 250 mL chilled cultured beverage for the adult market. The commercial concept is a product containing a quantified amount of vitamin K with a lawful bone- or coagulation-related function statement, provided the final formulation meets the relevant conditions. This is a design exercise, not a formula, clinical result or established commercial product of INTABIOTECH. It should begin with the exact supplier's MK-7 novel-food and vitamin-source status, confirmation that the intended food category is covered, and an assessment of likely consumers and co-formulated nutrients.

The first pilot could compare two legally suitable grades with different delivery vehicles while keeping the base beverage composition constant. In each grade, determine all-trans MK-7 by a validated method, identify relevant isomers and impurities, and calculate the vitamin introduced on an *active* rather than gross-premix basis. Formulate multiple independent batches at a target selected only after legal and nutritional assessment. For an illustrative nutritional declaration, a prototype may be designed around a target such as 75 µg vitamin K per serving, but this number is **not** presented as a recommended clinical dose or as automatic authorisation for a particular novel-food preparation.

The processing study should evaluate vitamin addition before and after homogenisation where technologically feasible, with controlled mixing duration, temperature, light and oxygen exposure. At a minimum, analyse post-mixing, post-heat-treatment, post-fermentation, filling and selected storage stages. Include between-bottle uniformity rather than assuming a well-mixed tank guarantees consistent delivered doses. For a live-culture product, microbial quality and fermentation performance should be monitored independently from vitamin recovery.

A stability study would follow at least several independently produced batches through the intended shelf life, with refrigeration and reasonably foreseeable temperature excursions. Primary analytical outcomes would be all-trans MK-7 per serving and product-specific microbial safety; important secondary outcomes would include geometric-isomer profile, pH, emulsion droplet size where relevant, sedimentation, oxidation markers, flavour and consumer acceptance. Packaging should be compared where oxygen or light barrier differences are expected to matter. An accelerated study may assist formulation selection, but real-time evidence must substantiate the declared shelf life.

A small food-level exposure study could compare the beverage with a reference presentation if the intended business objective includes a measurable difference in bioavailability. Such a study should use the same accurately assayed dose, predefined pharmacokinetic endpoints and appropriate controls. It should not be described as demonstrating a cardiovascular clinical effect. A separate patient-level trial would be necessary for such an outcome, and even a positive proprietary trial would not in itself amend the European claims register.

18. Minimum evidence package and stage-gated development

In practice, a technically differentiated MK-7 supplier should offer more than a certificate specifying vitamin percentage. A customer must be able to evaluate whether the ingredient is lawfully usable, whether it is chemically the intended material, whether the manufacturing process can reproduce it and whether it survives the customer's production line. This requires linking analytical and legal records to the same actual batch specification.

Table 4. Proposed industrial evidence package for an MK-7 ingredient platform

Evidence domain	Suggested documentation or test	Go/no-go decision
Production and provenance	Verified manufacturing organism or synthetic process, change control, traceability	Does supply match the material lawfully placed on the market?
Chemical identity	MK-7 homologue, all-trans/cis resolution, related menaquinones and impurity profile	Is the specified biologically relevant molecule present?
Quantitative assay	Validated chromatographic method, reference materials, recovery and uncertainty	Can delivered vitamin amounts be reliably reported?
Safety and interactions	Purity, process residues, microbiology as relevant, population exposure, vitamin K antagonists	Is the proposed use reasonably safe and suitably communicated?
Food processing	Mixing and fill homogeneity, heat, carrier, oxygen and light effects	Does MK-7 remain within specification during manufacture?
Shelf life	Real-time stability, packaging challenge, isomer profile, sensory and microbial quality	Is the finished dose stable until consumption?
Human evidence	Product-specific exposure, biomarkers and controlled outcomes where warranted	Which physiological statement can the evidence support?
European legal review	Union-list material identity, source permission, product category, claims and label	May this exact product and message be marketed?
Scale-up and economics	Independent lots, yield, purification losses, rejects, logistics and cost per compliant serving	Is the design viable beyond the laboratory?

The first gate should reject an ingredient whose legal identity does not match the proposed use. The second should demonstrate composition across independently manufactured lots. The third should confirm food-matrix compatibility and shelf life. The fourth should review communication and exposure before product launch. More ambitious clinical development should follow a defined evidence strategy rather than being used retrospectively to justify an already marketed message.

19. Computational tools can reduce wasted experiments, not substitute for assays

Manufacturing and formulation data are suitable for multivariate process engineering. Strain identity, substrate composition, oxygen transfer, fermentation time, extraction settings, carrier formulation, packaging and storage temperature may interact in determining all-trans MK-7 recovery. Statistical design of experiments can be used to identify response surfaces, and machine-learning systems may eventually help select batches or process conditions for deeper testing. These methods become valuable when they reduce rejected material, energy consumption or testing delay while maintaining food safety and product identity.

There is, however, a familiar risk of overfitting. Repeated injections of one extract are not independent fermentation batches. Data from one production run, even if sampled at many time points, cannot establish transferability across different strains, reactors or seasons. A predictive model should be evaluated on held-out manufacturing lots and, where intended for broader use, on new production facilities or suppliers. Analytical-method changes, different isomer separations and shifts in carrier composition should be recorded; otherwise, the algorithm may learn laboratory artefacts rather than manufacturing chemistry.

A more interesting application is decision optimisation under constraints. A model might rank candidate fermentation conditions by expected yield but exclude any condition associated with unacceptable impurity levels, poor stereochemical identity or questionable legal status. Similarly, a formulation optimiser could balance vitamin stability, cost and sensory acceptance without treating a favourable predicted score as permission to use an unapproved carrier or unsupported clinical claim. The role of computation is to make experimental design more efficient, not to replace measurement, toxicology or law.

20. The economics of an accurately specified vitamin

The commercial cost of MK-7 is commonly expressed per kilogram of concentrate or per unit of declared activity. Such figures can conceal substantial differences. One grade may contain a smaller fraction of the intended all-trans molecule; another may incur greater loss during heat treatment or storage; a third may require more expensive packaging or

additional premix preparation. The meaningful denominator is the cost per **saleable serving containing the verified target vitamin amount at the end of shelf life**.

For fermentation-derived supply, the cost structure includes substrate, energy, aeration, fermentation time, culture maintenance, extraction, purification, analytical quality control, rejected lots and product stability. Co-production may improve resource utilisation if both fractions are suitable for their intended markets, but it may also introduce separation complexity and reduce reproducibility. Economic models should calculate yield across the complete process, not select the most flattering titre from a laboratory broth.

The consequences of uncertainty are asymmetric. A batch that is slightly more expensive but legally well characterised and stable may be preferable to a nominally cheaper ingredient with poorly documented production provenance. For a customer producing large quantities of fortified foods, a supplier substitution that changes the legal status or assay response may impose significant recall, relabelling or revalidation costs. Evidence quality therefore has genuine commercial value as a component of supply reliability.

For INTABIOTECH, a credible opportunity would be the qualification of legally suitable MK-7 grades, evaluation of formulation technologies, coordination of analytical validation and support for compliant food-development programmes. This statement describes a possible research and ingredient-development direction, not a representation that the company has manufactured the vitamin, performed the cited trials or established product-specific clinical efficacy.

21. Discussion: precision in a field of encouraging but incomplete evidence

The MK-7 case is a valuable test of how ingredient science should handle simultaneously encouraging and incomplete evidence. Its chemistry is unusually well defined compared with many complex botanical extracts. Its microbial production can be engineered and measured. Its vitamin K–dependent pathway provides specific molecular hypotheses. And, in 2026, two randomised coronary studies reported favourable imaging outcomes. It would be an error to dismiss those results as merely another unverified supplement promise; it would be an equally serious error to treat them as a general authorisation to market cardiovascular protection.

The interaction among molecular identity, food manufacturing and human physiology provides an instructive reason for this dual conclusion. A trial can show an anatomical difference using a manufactured ingredient administered under controlled conditions. A commercial food, however, introduces variable carriers, processing, storage and consumer behaviours. The translation from an accurately dosed intervention to a lawful finished food is a manufacturing research task. The translation from an imaging difference to fewer clinical events is a medical research task. Neither follows automatically from the other.

The earlier neutral trials are equally important to interpretation because they show that pathway engagement is not sufficient across every disease state. Differences between coronary and valvular calcification, between patients with and without advanced renal dysfunction and between MK-7 monotherapy and K_2/D_3 combination therapy may be biologically meaningful. They also leave open several methodological explanations. This is a reason to design the next generation of trials around prespecified populations and outcomes, rather than to accumulate more loosely comparable biomarker studies.

European food law provides a useful framework for disciplined commercial translation. It recognises vitamin K as a legitimate nutrient with authorised general-function claims, while separately defining relevant source materials and demanding truthful consumer information. The law does not require that every scientific question be answered before a conventional nutrient claim can be used; nor does it permit companies to transform preliminary cardiovascular evidence into disease-treatment language. This separation is essential to innovation because it allows legitimate applications to proceed without overstating the science.

A modern industrial platform should therefore distinguish an MK-7 ingredient programme from an MK-7 clinical programme while allowing them to inform one another. The ingredient programme can establish purity, production consistency, lawful status, stability and reproducible exposure. The clinical programme can investigate biological response, imaging outcomes and eventually patient-relevant events. A company capable of documenting both chains without conflating them will be better positioned than one relying on a generic narrative of fermentation, “natural K_2” and broad cardiovascular promises.

22. Conclusions

Menaquinone-7 exemplifies a new class of familiar nutrients transformed by precision manufacturing. Its value begins with chemical specificity: the intended menaquinone homologue and geometrical form must be identified and quantified. Its industrial performance depends on production-strain control, downstream purification, reproducible assay, appropriate

carriers and finished-food stability. Its physiological interpretation depends on vitamin K–dependent carboxylation, systemic exposure and the distinction between biomarkers, imaging and clinical outcomes.

The 2026 VitaK-CAC and DANCODE trials provide substantive positive evidence of slower coronary-calcium progression in defined populations, although the latter studied combined MK-7 and vitamin D_3 and neither establishes cardiovascular-event prevention. Earlier neutral findings, particularly in some renal and valvular populations, remain part of the scientific record. Their coexistence calls for more precisely stratified trials rather than for premature certainty in either direction.

European law permits specified vitamin K function statements under defined nutritional conditions and provides a particular regulatory identity for novel-food menaquinone preparations. These permissions do not extend to every production process, every food category or unrestricted therapeutic language. For food-ingredient developers, the most durable advance will be a traceable evidence chain connecting the actual MK-7 molecule, a lawful and stable finished product, and only those consumer benefits that have been properly established and authorised.

References

1. Commission Decision 2009/345/EC of 22 April 2009 authorising the placing on the market of vitamin K_2 (menaquinone) from *Bacillus subtilis* natto as a novel food ingredient. *Official Journal of the European Union*. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32009D0345
2. Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017 establishing the Union list of novel foods under Regulation (EU) 2015/2283, as amended. *Official Journal of the European Union*. https://eur-lex.europa.eu/eli/reg_impl/2017/2470/oj
3. Commission Implementing Regulation (EU) 2018/1023 of 23 July 2018 correcting Implementing Regulation (EU) 2017/2470. *Official Journal of the European Union*. https://eur-lex.europa.eu/eli/reg_impl/2018/1023/oj
4. Commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods. *Official Journal of the European Union*. https://eur-lex.europa.eu/eli/reg/2012/432/oj
5. Cong, et al. (2025). Oral bioavailability enhancement of MK-7 from natto extract via HyperCelle nanoencapsulation in a clinical study. *Applied Biological Chemistry*, 68, 65. https://doi.org/10.1186/s13765-025-01043-4
6. DANCODE investigators. (2026). Vitamin K_2 and D_3 supplementation in patients with severe coronary artery calcification: The DANCODE trial. *Circulation*. https://doi.org/10.1161/CIRCULATIONAHA.126.082363
7. European Food Safety Authority, NDA Panel. (2017). Dietary reference values for vitamin K. *EFSA Journal*, 15(5), 4780. https://doi.org/10.2903/j.efsa.2017.4780
8. European Parliament and Council. (2002). Directive 2002/46/EC on the approximation of the laws of the Member States relating to food supplements, as amended. https://eur-lex.europa.eu/eli/dir/2002/46/oj
9. European Parliament and Council. (2002). Regulation (EC) No 178/2002 laying down the general principles and requirements of food law, as amended. https://eur-lex.europa.eu/eli/reg/2002/178/oj
10. European Parliament and Council. (2004). Regulation (EC) No 852/2004 on the hygiene of foodstuffs, as amended. https://eur-lex.europa.eu/eli/reg/2004/852/oj
11. European Parliament and Council. (2006). Regulation (EC) No 1924/2006 on nutrition and health claims made on foods, as amended. https://eur-lex.europa.eu/eli/reg/2006/1924/oj
12. European Parliament and Council. (2006). Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods, as amended. https://eur-lex.europa.eu/eli/reg/2006/1925/oj
13. European Parliament and Council. (2011). Regulation (EU) No 1169/2011 on the provision of food information to consumers, as amended, particularly Annex XIII. https://eur-lex.europa.eu/eli/reg/2011/1169/oj
14. European Parliament and Council. (2013). Regulation (EU) No 609/2013 on food intended for infants and young children, food for special medical purposes and total diet replacement, as amended. https://eur-lex.europa.eu/eli/reg/2013/609/oj
15. European Parliament and Council. (2015). Regulation (EU) 2015/2283 on novel foods, as amended. https://eur-lex.europa.eu/eli/reg/2015/2283/oj
16. Keyvan, E., et al. (2025). Vitamins formed by microorganisms in fermented foods: Effects on human vitamin status—a systematic narrative review. *Frontiers in Nutrition*, 12, 1653666. https://doi.org/10.3389/fnut.2025.1653666
17. Maneesha, & Subathra Devi. (2026). Co-production of nattokinase and menaquinone-7 from *Bacillus subtilis* MM26: A strain isolated from fermented grape wine. *Biotechnology Reports*. https://www.sciencedirect.com/science/article/abs/pii/S187881812600085X
18. National Health Service. (2024, updated online). Anticoagulant medicines: Considerations. https://www.nhs.uk/medicines/anticoagulants/considerations/
19. National Institutes of Health, Office of Dietary Supplements. (2026). Vitamin K: Fact sheet for health professionals. https://ods.od.nih.gov/factsheets/VitaminK-HealthProfessional/
20. Co-Production of Nattokinase and Menaquinone-7 by *Bacillus subtilis* Natto: Metabolic Trade-Offs, Regulatory Mechanisms, and Dynamic Fermentation Strategies. (2026). *Foods*, 15(21), 3869. https://doi.org/10.3390/foods15213869
21. Randomized Controlled Clinical Trial of the Effect of Treatment with Vitamin K_2 on Vascular Calcification in Hemodialysis Patients (Trevasc-HDK). (2023). PubMed record and linked primary publication. https://pubmed.ncbi.nlm.nih.gov/37705910/
22. Vitamin K and vascular calcification: From biological plausibility to clinical realism. (2026). *Clinical Kidney Journal*, 19(10), sfag249. https://doi.org/10.1093/ckj/sfag249

23. Vitamin K_2 and Cardiovascular Calcification: Mechanistic Foundations, Conflicting Clinical Evidence, and Unresolved Questions. (2026). *International Journal of Molecular Sciences*, 27(21), 9645. https://doi.org/10.3390/ijms27219645
24. Vossen, L. M., de Leeuw, P. W., Schurgers, L. J., Heuts, S., Adriaans, B. P., de Haan, C., van Varik, B. J., & Kroon, A. A. (2026). Two years of menaquinone-7 supplementation and coronary artery calcification: A randomized clinical trial. *JAMA Cardiology*, 11(8), 719–726. https://doi.org/10.1001/jamacardio.2026.1279
25. Effects of vitamin K_2 and D supplementation on coronary artery disease in men: A randomized controlled trial. (2023). *JACC: Advances*. https://pubmed.ncbi.nlm.nih.gov/38938724/
26. Coronary Artery Calcium Progression—A Useful Outcome in Clinical Trials? (2026). *JAMA Cardiology*, 11(8), 706–708. https://doi.org/10.1001/jamacardio.2026.1267

Editorial and evidentiary note. This critical narrative review integrates published studies, scientific interpretation and independent industrial and legal analysis. No research proposals are represented as completed INTABIOTECH experiments. Regulatory descriptions reflect instruments consulted through 19 November 2026; the current consolidated text, exact ingredient specification and relevant national requirements must be confirmed for each intended commercial use.

Copyright © 2026 José M. López. All rights reserved.