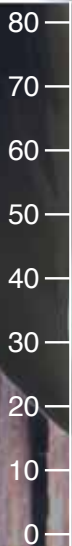


# Nutraceuticals Now

Winter 2014

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Olives

# STABILITY OF OILS AND FATS

# Vitamin K2, the “missing vitamin”

## ... now clinically-proven vital for bone and cardiovascular health

By Vladimir Badmaev MD, PhD, Head R&D NattoPharma ASA

The history of vitamin K illustrates a never-ending discovery of the use of the seemingly known nutritional compound. The importance of vitamin K, especially menaquinone-7 (vitamin MK-7) as a multitasking vitamin has been illuminated in the last five years, despite the fact that vitamin K has more than an 80-year-old history since its discovery. Vitamin K denotes a fat-soluble vitamin that occurs in two biologically active forms, phyloquinone (vitamin K1) and menaquinone (vitamin K2). Vitamin K1 is produced by plants and algae, and vitamin K2 is predominantly of microbial origin and comprises a family of molecules distinguished from K1 by unsaturated side chains of isoprenoid units varying in length from 1 to 14 repeats (hence, menaquinone-4, menaquinone-7 etc. or MK-4, MK-7).

The commonly recognized function of vitamin K is as a cofactor for  $\gamma$ -glutamylcarboxylase, an endoplasmic enzyme involved in the posttranslational carboxylation (activation) of proteins with glutamic acid (Glu) residues into  $\gamma$ -carboxyglutamate (Gla). With the carboxylation of glutamic acid residues on the protein substrate, a negative chemical group is formed that attracts and binds positively charged calcium. Calcium is a central element in the physiological role played by the Gla proteins; on the other hand calcium cannot be properly utilized by the body without Gla proteins and vitamin K. Vitamin K2 in particular is responsible for carboxylation and activation of osteocalcin, which is essential for bone building cells, osteoblasts. K2 helps in carboxylation and activation of another protein besides osteocalcin, matrix GLAprotein (MGP), for elasticity and prevention of calcification of blood vessels.

Despite the strong epidemiological evidence showing that dietary intake of vitamin K2 may improve overall health status, it was not until the three-year ‘breakthrough’ study of MenaQ7® brand – a natural supplement of K2 as MK-7 – that showed a significant health benefits with supplemental vitamin K (Osteoporosis Int. 2013).

The study was a double-blind randomized clinical trial evaluating the results of a three-year regular intake of natural MK-7 in a 180 mcg daily dose by a group of 244 healthy post-menopausal Dutch women, 55 to 65 years old. The outcome showed significant protection of the vertebrae and the hip (femoral neck) against osteoporosis and fractures due to osteoporosis and, for the first time, substantial benefits of nutritional vitamin K2, as compared to the placebo group, in preventing age-related stiffening of arteries manifested by a significant increase of the pulse wave velocity – a sign of aging and hardening of arterial walls (age-related calcification of arteries).

Enter the paradox of calcium: supplemental calcium is crucial for the maintenance of strong bones and cardiovascular system. On the other hand, several recent epidemiological studies – including the results of a 2013 JAMA-published study – indicate that supplemental calcium and vitamin D (which increases absorption of calcium) may be detrimental to cardiovascular health, presumably by increasing arterial calcification.

In view of the role of vitamin K as one of the most important biological compounds regulating calcium in the body, and the above cited three-year clinical study the new paradigm for supplemental calcium emerges, i.e. the guidelines for calcium supplements may have to be revised, and calcium and vitamin D supplements may need to be complemented with vitamin K2 due to vitamin K2’s increasingly recognized role as a calcium chaperone.

This emerging trend in vitamin K (K2’s MK-7 variety in particular) supplemental use has been further supported by the most recent clinical study in patients with chronic renal disease, evaluated for the cardiovascular effects of oral administration of vitamin K2 (MenaQ7 brand) plus vitamin D or vitamin D alone (Kurnatowska & Nowicki et al. 2013; 50th ERA-EDTA Congress). In this six-month study the progression of coronary artery calcification index (CAC) and common carotid intima media thickness (CCA-IMT) – both markers of calcium deposits in arteries detected with computerized tomography -- showed a slower progression of the calcification in the vitamin K2/vitamin D group than detected in the vitamin D-alone group of patients.

Historically, calcium and vitamin D supplementation are one of the most researched and sound nutritional combinations to strengthen the bone structure in infants, children, women, men and diverse racial or ethnic groups. Therefore, calcium and vitamin D supplements should not be avoided, but complemented with vitamin K2 supplementation; especially that recent epidemiological studies suggest that most healthy adults may be subclinically K2 insufficient – which results in K2-dependent proteins being biologically inactive in regulating calcium placement and utilization in the body.

In a recently published clinical study (Food&Function, 2013) the response to vitamin K2 supplementation was evaluated in populations of healthy children and middle aged and aging adults by measuring the levels of active and inactive K dependent proteins, osteocalcin and MGP respectively. The eight week supplementation with vitamin K2 improved status of active osteocalcin and MGP with outcome more pronounced in individuals with the initial higher levels of inactive K-dependent proteins. The authors of the study concluded that both children as well as adults above 40 years old may benefit from MK-7 supplementation to improve K-dependent proteins responsible for bone and cardiovascular health.

The current state of modern nutrition depletes sources of food-derived vitamin K2 and dietary supplementation of this vitamin is increasingly favored by the medical community. An effective supplemental vitamin K2 obtained in the fermentation process requires standardization for content, quality and stability. Through a significant innovation and multi-step purification process, the fermentation vitamin K2 up to 98,4% menaquinone-7, 100% trans- form, has been obtained in a crystal form (MenaQ7® Crystals). This natural MK-7 is backed by the above discussed three-year study demonstrating for the first time statistically significant improvements in bone and cardiovascular health status in a cohort of 244 healthy postmenopausal women.



# IFR

Institute of  
Food Research

## Consumer protection from misleading marketing

Since December 2012, any health claims on food packaging or used in advertising have to be authorised by the European Food Safety Authority (EFSA), to protect consumers from misleading, marketing. These claims have to be backed up by a large dossier of scientific evidence, but this has posed a problem to SMEs and other organisations without the resources or expertise to put together these evidence dossiers. Yet it is these SMEs who have been at the leading edge of nutraceutical innovation, raising concerns that the regulations are stifling new product development just at the time when healthier ingredients and diets are most needed.

To address this problem, the BACCHUS consortium formed, bringing together SMEs with leading food and health research organisations. Funded by the European Commission BACCHUS will help develop tools and techniques specifically aimed at helping SMEs generate dossiers of evidence for new foods or ingredients with demonstrable benefits for cardiovascular health. Cardiovascular disease is responsible for almost half of all deaths in the EU, so there is a need for any new nutraceuticals that could help reduce this. This also presents a significant business opportunity for innovation, depending on the quality of the evidence.

So what evidence is needed for health claims?

A growing body of evidence is showing that diets rich in polyphenols benefit cardiovascular health. But that’s not enough for a health claim. Claims must refer to a specific food or food component. The dossier must address three general areas: is characterisation of the food or food component sufficient? Is the claimed effect beneficial to human health? And, is there a cause-effect relationship between consumption and the claimed effect?

It is over the third of these where most polyphenol health claims have been rejected. Randomised, placebo-controlled studies in humans provide the best evidence, but these sorts of trials are hard and expensive to carry out. This is where BACCHUS will help. The expertise in the BACCHUS is helping to design experiments that align with EFSA’s requirements, for example in developing appropriate placebos and using relevant population groups.

BACCHUS is also helping ensure potential nutraceutical foods are properly characterised. Foods aren’t like drugs, they consist of many different compounds with different potentially bioactivities. BACCHUS is ensuring the characterisation of polyphenols in these complex foods is sufficiently rigorous. Polyphenols are often modified as they are taken up by the body, if they are indeed absorbed at all. The members of the BACCHUS consortium have expertise in understanding this bioavailability – is the compound taken up in sufficient quantities and in a metabolised form to have a genuine effect in the body? Without knowing this,

there is little chance of getting a mechanistic understanding of potential health benefits.

Identifying the bioavailable, bioactive form of a food ingredient is key to working out how these compounds interact with our bodies and bring about potential health benefits. A mechanism describing how an ingredient affects health in humans is essential for health claim approval. BACCHUS will identify these mechanisms for a number of bioactive peptides and polyphenols linking together, scientifically, the consumption of food ingredients with health benefits.

BACCHUS is looking at a number of polyphenols that have already been identified as having possible beneficial benefits to cardiovascular health. The focus is on just a handful of these, in effect using them as case studies. Flavanols from apples are an example. Studies have shown already that apple flavanols are bioavailable. The BACCHUS project will look at whether they can reduce blood pressure, and whether they can be delivered in effective dosages. If so there is good potential for the development of apple flavanol based nutraceuticals.

The longer term aim of BACCHUS is learn from case studies like this to develop best practice in evidence gathering for gold-standard health claims. This will be made available more widely through training sessions and advice targeted to the food industry. At the same time this will boost the scientific understanding of the links between food and human health, and give us all the best chance of seeing new products on supermarket shelves that benefit us all.

**BACCHUS is a four-year FP7-KBBE-funded Collaborative (Research) Project, targeted at a special group, with 28 beneficiaries including 16 Small and Medium Enterprises (SME) from 11 countries, led by the Institute of Food Research (IFR, UK). To find out more please see: <http://www.bacchus-fp7.eu/>**