This scientific information is intended for healthcare professionals.

Therapeutic use of Omega-3 + Vitamin K_2 + D_3 + Ubiquinol

- EPA and DHA help maintain normal **blood pressure**[1], normal **triglyceride levels**[2] and normal function of the **heart**[3]
- Vitamin K_2 helps maintain normal bones, and contributes to normal blood clotting.
- Vitamin D_3 helps maintain normal **bones**, and contributes to normal blood **calcium levels** and the maintenance of the normal function of **muscles** and the **immune system**
- Ubiquinol is a physiological substance present in all body cells

With a daily intake of (1) 3 g EPA+DHA, (2) 2 g EPA+DHA, (3) at least 250 mg EPA+DHA

Applications and recommended use

Supporting cardiovascular health

Supporting vitality, sustainable energy production

Maintenance of strong bones and healthy muscles

Immune system support

Vitamin D for individuals with inadequate sunlight exposure (nursing homes, use of high UV protection factor, during winter)

Protection against oxidative stress (anti-ageing)

Partner in recreational and competitive sports

Typical indications for EPA+DHA:

Secondary prevention of myocardial infarction
Ventricular arrhythmia induced by oxygen deficiency
Chronic heart failure
Prevention atrial fibrillation after bypass-surgery
Hypertriglyceridemia
Hypertension

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Typical indications for vitamin K_2 with vitamin D_3:

Prevention atherosclerotic plaque calcifications

Postmenopausal osteoporosis

Fall prevention in the elderly

Immune system weakening (e.g. flu prevention)

Discomforts due to proven vitamin D deficiency (muscle pain, hypertension, memory problems, depressive symptoms)

Typical indications for ubiquinol:

Prevention of LDL-cholesterol oxidation

Congestive heart failure

Hypertension

Diabetes type 2

Male fertility problems

Migraine

Fibromyalgia

Chronic fatigue syndrome

Neurodegenerative diseases (Alzheimer's disease, Parkinson's disease)

Combination with drugs

May be combined with a cardio-aspirin, ß-blockers, ACE-inhibitors, fibrates, sartans, diuretics and/or statins.

Interactions and precautions

The European Food Safety Authority (EFSA) considers the long-term use of **5 g EPA+DHA/day** to be safe for adults, **without increasing the risk of spontaneous bleeding or bleeding complications** (even with concomitant use of low-dose acetylsalicylic acid or anti-coagulants).[1]

Omega-3 fatty acids do **not** have a **clinically relevant effect on LDL cholesterol levels**. At daily doses of 2-6 g EPA+DHA may induce a small increase in LDL-cholesterol concentrations of about 3%, which does not have an adverse effect on cardiovascular disease risk.[1]

Omega-3 fatty acids do not have a clinically relevant effect on blood sugar control (no changes in HbA1c, possibly small increases of 2-6 mg/dl in fasting glucose).[2-4]

Daily supplementation with as little as 10 µg MK-7 may significantly disturb a protocol with anticoagulants in some individuals.[21] In adults who did not use any anticoagulants, MK-7 in doses up to 360 µg per day gave no indications towards an increased risk of developing thrombosis.[19]

Ubiquinol may enhance the action of antidiabetic and blood-pressure-lowering drugs. Monitoring is therefore recommended during concomitant use.

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Scientific information

EPA/DHA as cardiovascular protection

The cardiovascular health benefits of EPA and DHA vary from modulations in endothelial functions (through prostaglandin homeostasis, relaxation of the blood vessel wall, induction of less atherogenic LDL particles and improved plaque stability) to antiarrhythmic effects (shifts in the voltage potential of cardiac muscle cells, reduced risk of ventricular fibrillation in response to oxygen deficiency, increased heart rate variability, better cardiac muscle adaptation capacity).[5-7]

According to the advice of the **European Society of Cardiology** cardiac patients preferably use **~1 g EPA+DHA per day** after a recent **heart attack** as well as in cases of **chronic heart failure**.[8]

The cardiac patients (n = 11323) who were eligible to participate to the Italian GISSI Prevenzione study had, at the earliest 3 months before, suffered a heart attack. For 3.5 years they used ~1 g EPA+DHA (EPA/DHA ratio = 1.2/1) per day on top of their conventional treatments (blood thinner, blood pressure-lowering drug, cholesterol-lowering medicine). Thanks to the omega-3 supplementation their risk of sudden death was reduced with 45%.[9-12] In the placebo-controlled GISSI-HF study patients with chronic heart failure (irrespective of the left ventricular ejection fraction) (n = 3494) used ~1 g EPA+DHA/dag (EPA/DHA ratio = 1.2/1) per day. The researchers came to the final conclusion that thanks to the omega-3 supplementation per 1000 patients 18 lives were saved and 17 hospitalizations due to cardiovascular problems were prevented.[13]

Patients who needed to undergo **bypass-surgery** (n=79) used ~2 g EPA+DHA/day (EPA/DHA ratio = 1.2/1) in a placebo-controlled trial setting from 5 days before surgery until discharge from the hospital. Thanks to the omega-3 supplementation patients had a shorter hospital stay (p = 0,017) and a 54.4% reduced risk of experiencing postoperative atrial fibrillation (p = 0,013).[14]

In hyperlipidaemic patients (n = 16511) with a mean **triglyceride level** of 216 mg/dl supplementation with 3.25 g EPA+DHA per day on average induced a reduction in triglyceride levels of 40 mg/dl.[15] A severely elevated triglyceride level (> 500 mg/dl) can be lowered by 45% with a dose of 3-4 g EPA+DHA/day.[16]

In patients with hypertension supplementation with at least 3.3 g EPA+DHA per day (n = 1356) was able to reduce systolic and diastolic **blood pressure with** 2.9 and 1.6 mm Hg, respectively.[17] The strongest effects of EPA+DHA supplementation were observed in untreated hypertensive patients: reductions of 4.51 mm Hg and 3.05 mm Hg in systolic and diastolic blood pressure, respectively.[18]

Differences in the type of vitamin K

Vitamin K (K_1 and K_2) functions as a cofactor in the synthesis of **blood clotting factors** in the liver. It is the most important function for vitamin K_1 (a short molecule found in green vegetables). For vitamin K's extrahepatic functions the **vitamin K_2s** (the longer molecules) are more potent than vitamin K_1: they are carried on LDL-cholesterol particles that bring them into contact with the **blood vessel wall** and the **bone matrix** (see further). Menaquinone 7 (MK-7) is the vitamin K_2 that is highly concentrated in natto, a typical Japanese breakfast of cooked, fermented soybeans. A 40 g standard portion of natto contains approximately 350 µg MK-7.[22] Why is MK-7 so beneficial? MK-7 stays in the bloodstream for a long time (half-life of 3 days contrary to 1 hour for vitamin K_1), with MK-7 a high plasma concentration is reached (7 to 8 times higher than

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with vitamin K_1) and in extrahepatic tissues MK-7 is already therapeutically active in low doses (doses in the order of µg per day contrary to doses in the order of mg per day for menaquinone 4 or MK-4, the vitamin K_2 from meat/eggs/liver).[23-26]

Vitamin K_2 **prevents the calcification of atherosclerotic plaques** and has a role in **bone mineralisation**. In the blood vessel wall vitamin K_2 acts as a cofactor in the carboxylation of Matrix Gla Protein (MGP). MGP accumulates around elastin fibres in the blood vessel wall and is the strongest inhibitor of the calcification process. Once carboxylated, MGP binds calcium and by doing this prevents calcium from being deposited in the blood vessel wall.[26] In the bone structures vitamin K_2 acts as a cofactor in the carboxylation of osteocalcin, a protein that is synthesized by the bone-forming cells. Once carboxylated, osteocalcin binds calcium and supports the incorporation of calcium into the hydroxyapatite component of the bone matrix.[27]

Research showed that after supplementation with MK-7 more carboxylated osteocalcin could be measured in both adults (90 µg/d)[19,20] and children (mean age of 8 years, 45 µg/d)[28], which indicates an improved potential to incorporate calcium into bone tissue. A placebo-controlled trial in 244 postmenopausal women confirmed a positive effect on bone mineral content and bone mineral density at the lumbar spine and femoral neck after supplementation with MK-7 (180 µg/d) for 3 years. Moreover, MK-7 supplementation also decreased the loss in vertical length at the thoracic region.[29]

In research performed at the universities of Maastricht and Utrecht (The Netherlands) scientists detected improvements in carboxylated MPG upon us of MK-7 (180-360 µg/d) in adults, which indicates an improved potential to prevent a deposition of calcium in the blood vessel wall.[30] In the Prospect-EPIC study in over 16000 postmenopausal women it was shown that the dietary of vitamin K_2 (MK-7, MK-8, MK-9) – but not of vitamin K_1 – could protect against coronary heart disease.[31]

Cholecalciferol as most effective vitamin D

Vitamin D is available as vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Various research data have already demonstrated that ergocalciferol has a lower affinity for the vitamin D receptor, poorer stability and shorter duration of action than cholecalciferol, resulting in a 33% lower efficiency.[32-34]

Vitamin D facilitates the intestinal absorption of calcium, making it important for **calcium homeostasis** and the maintenance of strong bones. Moreover, vitamin D is associated with several physiological systems outside the skeleton: **immune system**, **heart muscle** functioning, **blood pressure regulation** (via the renin-angiotensin system), pancreatic ß cells (promotion of **insulin secretion**), musculature (**fall prevention**).[35] Serum calcidiol levels are measured to determine an individual's vitamin D status. The minimal target value is 50 nmol/l (20 ng/ml), but 75 nmol/l (30 ng/ml) might even be better to experience the full range of health benefits of vitamin D.[36-40] To reach a serum calcidiol level of 75 nmol/l a dosage of 25-50 µg/d (1000-2000 IU/d) is usually needed.[38,39]

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Ubiquinol, the ready-to-use antioxidant of co-enzyme Q10

Coenzyme Q10 (coQ10) is the rate-limiting cofactor in **cellular energy** production. Within the body coQ10 exists as a redox couple containing ubiquinol (reduced form) and ubiquinone (oxidized form). A physiological predominance of ubiquinol is enzymatically maintained: ubiquinol represents up to > 80% of the total coenzyme Q10 pool. Ubiquinol is the antioxidant form of the couple.

In the elderly and in case of diseases (COPD, Parkinson's disease, heart failure, liver diseases) the proportion of ubiquinone in plasma significantly increases at the expense of ubiquinol. This phenomenon results from an increase in oxidative stress, a reduced conversion of ubiquinone into ubiquinol, or both. In order to restore the physiological balance between ubiquinone and ubiquinol it is recommended to directly consume ubiquinol.[41-43]

In terms of cardiovascular health ubiquinol inhibits **LDL cholesterol oxidation**[44], and contributes to an improved **contraction force of the heart**[45], a **reduction** in **elevated blood pressure**[46] and adequate **sugar metabolism** (improved insulin secretion)[47].

Because of its antioxidant capacity, amongst other features, ubiquinol also has a positive impact on **male fertility** (improved sperm density and motility)[48], the quality of life in **fibromyalgia** and **CFS**[49-51], the frequency of **migraine**[52], and potentially on the repair of **gum tissue** (in case of periodontitis)[53].

References

1. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion related to the Tolerable Upper Intake Level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). EFSA Journal 2012;10(7):2815.
2. Hartweg J, Perera R, Montori V, Dinneen S, Neil HA, Farmer A. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. Cochrane Database Syst Rev 2008; (1):CD003205.
3. Maki KC, Lawless AL, Kelley KM, Dicklin MR, Schild AL, Rains TM. Prescription omega-3-acid ethyl esters reduce fasting and postprandial triglycerides and modestly reduce pancreatic ß-cell response in subjects with primary hypertriglyceridemia. Prostaglandins Leukot Essent Fatty Acids 2011; 85(3-4):143-8.
4. Jeppesen C, Schiller K, Schulze MB. Omega-3 and omega-6 fatty acids and type 2 diabetes. Curr Diab Rep 2013; 13(2):279-88.
5. Rupp H. Omacor (prescription omega-3-acid ethyl esters 90): From severe rhythm disorders to hypertriglyceridemia. Adv Ther 2009; 26(7):675-90.
6. Cheng JW, Santoni F. Omega-3 fatty acid: a role in the management of cardiac arrhythmias? J Altern Complement Med 2008; 14(8):965-74.
7. Lavie CJ, Milani RV, Mehra MR, Ventura HO. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. J Am Coll Cardiol. 2009; 54(7):585-94.
8. Kromhout D, Yasuda S, Geleijnse JM, Shimokawa H. Fish oil and omega-3 fatty acids in cardiovascular disease: do they really work? Eur Heart J 2012; 33(4):436-43.
9. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999; 354(9177):447-55.
10. Marchioli R, Levantesi G, Macchia A, Maggioni AP, Marfisi RM, Silletta MG, Tavazzi L, Tognoni G, Valagussa F; GISSI-Prevenzione Investigators. Antiarrhythmic mechanisms of n-3 PUFA and the results of the GISSI-Prevenzione trial. J Membr Biol 2005; 206(2):117-28.
11. Bays H. Clinical overview of Omacor: a concentrated formulation of omega-3 polyunsaturated fatty acids. Am J Cardiol 2006; 98(4A):71i-76i.
12. Bays H. Fish oil composition of Omacor and the GISSI trial. Am J Cardiol 2007; 99(10):1483-4.
13. Gissi-HF Investigators, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, Latini R, Lucci D, Nicolosi GL, Porcu M, Tognoni G. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008; 372(9645):1223-30.

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14. Calò L, Bianconi L, Colivicchi F, Lamberti F, Loricchio ML, de Ruvo E, Meo A, Pandozi C, Staibano M, Santini M. N-3 Fatty acids for the prevention of atrial fibrillation after coronary artery bypass surgery: a randomized, controlled trial. J Am Coll Cardiol 2005; 45(10):1723-8.
15. Eslick GD, Howe PR, Smith C, Priest R, Bensoussan A. Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis. Int J Cardiol 2009; 136(1):4-16.
16. Lavie CJ, Milani RV, Mehra MR, Ventura HO. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. J Am Coll Cardiol. 2009; 54(7):585-94.
17. Morris MC, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. Circulation 1993; 88(2):523-33.
18. Miller PE, Van Elswyk M, Alexander DD. Long-Chain Omega-3 Fatty Acids Eicosapentaenoic Acid and Docosahexaenoic Acid and Blood Pressure: A Meta-Analysis of Randomized Controlled Trials. Am J Hypertens. 2014 Mar 6.
19. Theuwissen E, Cranenburg EC, Knapen MH, Magdeleyns EJ, Teunissen KJ, Schurgers LJ, Smit E, Vermeer C. Low-dose menaquinone-7 supplementation improved extra-hepatic vitamin K status, but had no effect on thrombin generation in healthy subjects. Br J Nutr 2012; 108(9):1652-7.
20. Brugè F, Bacchetti T, Principi F, Littarru GP, Tiano L. Olive oil supplemented with menaquinone-7 significantly affects osteocalcin carboxylation. Br J Nutr 2011; 106(7):1058-62.
21. Theuwissen E, Teunissen KJ, Spronk HM, Hamulyák K, Ten Cate H, Shearer MJ, Vermeer C, Schurgers LJ. Effect of low-dose supplements of menaquinone-7 (vitamin K2) on the stability of oral anticoagulant treatment: dose-response relationship in healthy volunteers. J Thromb Haemost 2013; 11(6):1085-92.
22. Ikeda Y, Iki M, Morita A, Kajita E, Kagamimori S, Kagawa Y, Yoneshima H. Intake of fermented soybeans, natto, is associated with reduced bone loss in postmenopausal women: Japanese Population-Based Osteoporosis (JPOS) Study. J Nutr. 2006 May;136(5):1323-8.
23. Schurgers LJ, Teunissen KJ, Hamulyák K, Knapen MH, Vik H, Vermeer C. Vitamin K-containing dietary supplements: comparison of synthetic vitamin K1 and natto-derived menaquinone-7. Blood 2007; 109(8):3279-83.
24. Knapen MH, Schurgers LJ, Vermeer C. Vitamin K2 supplementation improves hip bone geometry and bone strength indices in postmenopausal women. Osteoporos Int 2007; 18(7):963-72.
25. Ikeda Y, Iki M, Morita A, Kajita E, Kagamimori S, Kagawa Y, Yoneshima H. Intake of fermented soybeans, natto, is associated with reduced bone loss in postmenopausal women: Japanese Population-Based Osteoporosis (JPOS) Study. J Nutr 2006; 136(5):1323-8.
26. Cranenburg EC, Schurgers LJ, Vermeer C. Vitamin K: the coagulation vitamin that became omnipotent. Thromb Haemost 2007; 98(1):120-5.
27. Yamaguchi M. Regulatory mechanism of food factors in bone metabolism and prevention of osteoporosis. Yakugaku Zasshi 2006; 126(11):1117-37.
28. van Summeren MJ, Braam LA, Lilien MR, Schurgers LJ, Kuis W, Vermeer C. The effect of menaquinone-7 (vitamin K2) supplementation on osteocalcin carboxylation in healthy prepubertal children. Br J Nutr. 2009; 102(8):1171-8.
29. Knapen MH, Drummen NE, Smit E, Vermeer C, Theuwissen E. Three-year low-dose menaquinone-7 supplementation helps decrease bone loss in healthy postmenopausal women. Osteoporos Int 2013; 24(9):2499-507.
30. Dalmeijer GW, van der Schouw YT, Magdeleyns E, Ahmed N, Vermeer C, Beulens JW. The effect of menaquinone-7 supplementation on circulating species of matrix Gla protein. Atherosclerosis 2012; 225(2):397-402.
31. Gast GC, de Roos NM, Sluijs I, Bots ML, Beulens JW, Geleijnse JM, Witteman JC, Grobbee DE, Peeters PH, van der Schouw YT. A high menaquinone intake reduces the incidence of coronary heart disease. Nutr Metab Cardiovasc Dis 2009; 19(7):504-10.
32. Bouillon R. Genetic and environmental determinants of vitamin D status. Lancet 2010; 376(9736):148-9.
33. Zarowitz BJ. The value of vitamin D(3) over vitamin D(2) in older persons. Geriatr Nurs 2008; 29(2):89-91.
34. Heany RP. Vitamin D in health and disease. Clin J Am Soc Nephrol 2008; 3:1535-41.
35. Barnard K, Colón-Emeric C. Extraskeletal effects of vitamin D in older adults: cardiovascular disease, mortality, mood, and cognition. Am J Geriatr Pharmacother 2010; 8(1):4-33.
36. Neuprez A, Bruyère O, Collette J, Reginster JY. Vitamin D inadequacy in Belgian postmenopausal osteoporotic women. BMC Public Health 2007;7:64.
37. Failla V, Cavalier E, El Hayderi L, Paurobally D, Chapelle JP, Dezfoulian B, Nikkels AF. Seasonal variations in vitamin D levels in melanoma patients: a single-centre prospective pilot comparative study. J Eur Acad Dermatol Venereol 2012; 26(5):651-3.

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38. Cianferotti L, Marcocci C. Subclinical vitamin D deficiency. Best Practice & Research Clinical Endocrinology & Metabolism 2012; 26:523–37.
39. Wimalawansa SJ. Vitamin D in the new millennium. Curr Osteoporos Rep 2012; 10(1):4-15.
40. Verhoeven V, Vanpuyenbroeck K, Lopez-Hartmann M, Wens J, Remmen R. Walk on the sunny side of life--epidemiology of hypovitaminosis D and mental health in elderly nursing home residents. J Nutr Health Aging 2012; 16(4):417-20.
41. Wada H, Goto H, Hagiwara S, Yamamoto Y. Redox status of coenzyme Q10 is associated with chronological age. Am Geriatr Soc 2007; 55(7):1141-2.
42. Yamamoto Y, Yamashita S. Plasma ubiquinone to ubiquinol ratio in patients with hepatitis, cirrhosis, and hepatoma, and in patients treated with percutaneous translu¬minal coronary reperfusion. Biofactors 1999; 9(2-4):241-6.
43. Yan J, Fujii K, Yao J, Kishida H, Hosoe K, Sawashita J, Takeda T, Mori M, Higuchi K. Reduced coenzyme Q10 supplementation decelerates senescence in SAMP1 mice. Exp Gerontol 2006; 41(2):130-40.
44. Garrido-Maraver J, Cordero MD, Oropesa-Ávila M, Vega AF, de la Mata M, Pavón AD, de Miguel M, Calero CP, Paz MV, Cotán D, Sánchez-Alcázar JA. Coenzyme Q 10 Therapy. Mol Syndromol 2014; 5:187–97.
45. Langsjoen PH, Langsjoen AM. Supplemental ubiquinol in patients with advanced congestive heart failure. Biofactors 2008; 32(1-4):119-28.
46. Rosenfeldt FL, Haas SJ, Krum H et al. Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials. J Hum Hypertens 2007; 21(4):297-306.
47. Mezawa M, Takemoto M, Onishi S, Ishibashi R, Ishikawa T, Yamaga M, Fujimoto M, Okabe E, He P, Kobayashi K, Yokote K. The reduced form of coenzyme Q10 improves glycemic control in patients with type 2 diabetes: an open label pilot study. Biofactors 2012; 38(6):416-21.
48. Safarinejad MR, Safarinejad S, Shafiei N, Safarinejad S. Effects of the reduced form of coenzyme q(10) (ubiquinol) on semen parameters in men with idiopathic infertility: a double-blind, placebo controlled, randomized study. J Urol 2012; 188(2):526-31.
49. Miyamae T, Seki M, Naga T, Uchino S, Asazuma H, Yoshida T, Iizuka Y, Kikuchi M, Imagawa T, Natsumeda Y, Yokota S, Yamamoto Y. Increased oxidative stress and coenzyme Q10 deficiency in juvenile fibromyalgia: amelioration of hypercholesterolemia and fatigue by ubiquinol-10 supplementation. Redox Rep 2013;18(1):12-9.
50. Alcocer-Gómez E, Sánchez-Alcázar JA, Cordero MD. Coenzyme q10 regulates serotonin levels and depressive symptoms in fibromyalgia patients: results of a small clinical trial. J Clin Psychopharmacol 2014; 34(2):277-8.
51. Alcocer-Gómez E, Sánchez-Alcázar JA, Cordero MD. Coenzyme q10 regulates serotonin levels and depressive symptoms in fibromyalgia patients: results of a small clinical trial. J Clin Psychopharmacol 2014; 34(2):277-8.
52. Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Coenzyme Q10 deficiency in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is related to fatigue, autonomic and neurocognitive symptoms and is another risk factor explaining the early mortality in ME/CFS due to cardiovascular disorder. Neuro Endocrinol Lett. 2009;30(4):470-6. Neuro Endocrinol Lett 2009;30(4):470-6.
53. Rozen TD, Oshinsky ML, Gebeline CA, Bradley KC, Young WB, et al: Open label trial of coenzyme Q10 as a migraine preventive. Cephalalgia 2002; 22:137-41.
54. Wilkinson EG, Arnold RM, Folkers K. Bioenergetics in clinical medicine. VI. adjunctive treatment of periodontal disease with coenzyme Q10. Res Commun Chem Pathol Pharmacol 1975; 12(1):111-24.

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