

Dietary Supplements: Beneficial to Human Health or Just Peace of Mind? A Critical Review on the Issue of Benefit/ Risk of Dietary Supplements

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Summary. Dietary supplement can be defined as any vitamin, mineral, added chemical substances, botanical or herbal products that is added to the diet to improve human health. Scientists and health professionals agree that dietary supplements can be under certain conditions beneficial to human health, but should not replace complete and balanced daily meals of foods which are necessary for a healthful diet. The most authoritative national agency U.S. Food and Drug Administration (FDA) emphasized that "...*unlike drugs, dietary supplements are not intended to treat, diagnose, prevent, or cure diseases. Dietary supplements should not make claims, such as "reduces pain" or "treats heart disease", etc...*". Globally, dietary supplement market stood at over US\$90 billion in 2013, and on top is the US market with over 30 billion every year. For many years informed medical sources like doctors, nurses, pharmacists, nutritionists and medical authorities agree that there's a lot of wrong information in the supplements market. Many dietary supplements, even in the USA that has some of the most experienced health agencies, managed to escape the safety tests, labeling and health regulations. From 2007, some of the most well known scientists in the USA on nutrition, metabolism and epidemiology reviewed the evidence on multivitamin/mineral supplements and concluded that there was not sufficient evidence to recommend for or against for the prevention of chronic disease. Randomized Control Trials of dietary supplements increased substantially in the last decade in many developed countries. The results are mixed but the majority is negative for health benefits or for preventing diseases. In 2013 three papers and an overall review of the results for the last decade with the title "*Enough is enough. Stop wasting money on vitamin and mineral supplements*" was published in the prestigious medical journal *Annals of Internal Medicine* in the USA. The influence of these research results was spread to other developed countries and more critical appraisals were published on dietary supplements. This review covers the most important aspects of dietary supplements, the trends in global market, the national and international regulations of various products. Also, examines the debate and arguments of health professionals. The review examines in a systematic way the most important studies that were published in the scientific literature in the last few years on the most widespread dietary supplements and their results on benefits or risk to human health. It covers dietary supplements taken by young, elderly, pregnant women, athletes and people with deficiencies which were self-prescribed and on the international market.

KEY WORDS : Dietary Supplements, Balancer Diet, Vitamins, Minerals, Randomized Control Trials, Health Benefit, Risk, Global Dietary Supplements Market

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1. Introduction : balanced diet and dietary supplements

Dietary supplement can be defined as any vitamin, mineral, added chemical substance, herbal product, botanicals, amino acids, or other ingestible preparation that is added to the diet to benefit human health. Dietary supplements are used worldwide and represent a broad category of ingestible products that are distinguishable from conventional foods and drugs.¹⁻⁵

All developed countries have special legislation concerning dietary supplement (for example, U.S. Dietary Supplement Health and Education Act, 1994). In countries, such as Australia and Canada,

dietary supplements and drugs are regulated similarly, and only ingredients deemed acceptable by the Therapeutic Goods Administration of Australia or the Natural Health Products Directorate of Canada can be sold as dietary supplements. In the European Union (EU), dietary supplement regulations (Directive 2002/46/EC) often follow a case-by-case basis, depending upon the individual country and the available safety evidence for the ingredient. In China, India and Japan, where plants, herbs, botanicals and animal extracts have a long history of use as traditional medicine, regulations are different but relatively stringent in terms of safety and side effects to humans.⁶⁻¹¹ Japan has no legal definition of dietary supplements, mostly are classified into food products or drugs. The Ministry of Health and Welfare set up the Food for Specified Health Uses (FOSHU) to provide people with accurate health information about dietary supplements and the current Japanese system for regulation of health foods is called Food with Health Claims and is made up of two categories: “Food with Nutrient Function Claims” and “Food for Specified Health Uses”.¹²



The Healthy Eating Pyramid



Figure 1. Conventional, balanced and healthy eating can cover all needs of the human body in terms of energy, basic nutrients (carbohydrates, proteins, fatty acids, water) and micronutrients (vitamins, minerals, antioxidants, etc).

A fundamental question that everybody asks these days that most people are very aware that nutrition plays a very important role in health is, if conventional, balanced and without supplements diet can cover all the needs of the human body for a healthy lifestyle until old age. Nutritionists and health professionals argued for years that people can get the most important food requirements that their body needs each day from a conventional, balanced and regular daily diet. Today’s dietary guidelines from health and nutrition agencies cover more than 40 nutrients that are subdivided into 6 categories: carbohydrates, fats, proteins, vitamins, minerals and water. Daily nutrient recommendations are collectively known as dietary reference intakes (DRIs). A healthy diet is one that favours “real” fresh whole foods that have been sustaining people throughout the millenniums. Whole foods supply the needed vitamins, minerals, protein, carbohydrates, fats, and fiber that are essential to good health. In contrast, commercially prepared and fast foods are often lacking nutrients and contain inordinate amounts of sugar, salt, saturated and trans-fats, all of which are associated with the development of diseases. A balanced diet is a mix of food from the different food groups (vegetables, legumes, fruits, grains, protein foods, meat, and dairy). Variety involves eating different foods from all the food groups that helps to ensure that you receive all the nutrients necessary for a healthy diet. The components of the Mediterranean diet have been evaluated as substantially beneficial to human health.¹³⁻¹⁵

The World Health Organization (WHO) makes the following recommendations for a balanced and healthy diet: a. eat roughly the same amount of calories that your body is using, b. a healthy weight is a balance between energy consumed and energy that is 'burnt off', c. limit intake of fats, and prefer unsaturated, than saturated fats and trans fats, d. increase consumption of plant foods, particularly fruits, vegetables, legumes, whole grains and nuts, e. limit the intake of sugar, salt/sodium consumption from all sources and ensure that salt is iodized, f. eat a diet with essential micronutrients such as vitamins and certain minerals.^{16,17}

2. Dietary supplements: short historical overview

From the beginning of human civilization diet was mostly plant foods that could be easily gathered and seafoods. Hunter-gatherers later contributed meat products by big game. This was the diet of most humans until about 10,000 BC, at which time the development of agriculture and animal husbandry provided more meat and grains for the whole family. Nobody knew about vitamins, minerals, proteins, carbohydrates and fats and their role in human nutrition. The various people in the continents of the Earth developed nutritious local cuisines with mostly local products that sustained their health, whereas by trial and error choose a variety of foods and cooking methods that lead to physical strength, health, and fertility. The common wisdom of native cultures knew which foods and herbs had special properties for energy, nutrition and extra health benefits for children, pregnant women and elders. Everyday diets were "supplemented" to make up for deficiencies as far back as native cultures. Native Americans, for example, knew to drink a tea made from pine bark and needles for scurvy containing high concentration of ascorbic acid, which was later found by science to be a vitamin C deficiency disease. In 1749, Dr. James Lind discovered citrus fruits prevented scurvy (high in vitamin C content).¹⁸⁻²⁰

The discovery of the role of vitamins was a major scientific achievement in the understanding on the association of nutrition, health and disease. By the 1920s and 1930s, significant strides were being made in the world of vitamin research and mass marketing (synthesized vitamin C in 1935 and marketed as vitamin C supplement under the name Redoxon). In the nearly 75 years since the vitamin C pill was marketed, large steps have been made in the vitamin and other dietary supplement products. Increased public interest was stimulated as a result of claims (proved to be false later) made in the USA by Nobel-laureate Linus Pauling (1901-1994) in the 1970s, that "megadoses" of at least 10 times the RDA (Recommended Dietary Allowances) of ascorbic acid could prevent or cure the common cold, flu, and cancer.²¹ In 1976, Pauling and Dr. E. Cameron contacted experiments and reported that a majority of 100 "terminal" cancer patients treated with 10,000 mg of vitamin C daily survived three to four times longer than similar patients who did not receive vitamin C supplements. Nevertheless, to test whether Pauling might be correct, the Mayo Clinic conducted three double-blind studies involving a total of 367 patients with advanced cancer. The studies, reported in 1979, 1983, and 1985, found that patients given 10,000 mg of vitamin C daily did no better than those given a placebo.²²⁻²⁵ In fact, recent laboratory studies have found that vitamin C may interfere with the effectiveness of five anti-cancer drugs.²⁶

Although health claims for a variety of vitamin supplements proved to be controversial, popular books, consumer and sport magazines, popular newspapers and TV advertisements in developed countries advertise spurious claims for various botanical herbs, and constituents of food for health benefits and "magical" cures for a variety of diseases. The majority of these claims are not supported by scientific studies. The mainstream scientific community gradually became intrigued by the potential health benefits of dietary supplements and numerous research projects (epidemiologic, clinical, *in vivo* and *in vitro*) were initiated in the 1980s. This interest was fueled in part by studies demonstrating that nutrient antioxidants, (vitamins C and A, E and b-carotene, Selenium), have a role in protecting cells

from oxidative free radical damage. Furthermore, epidemiological studies suggested that a diet rich in fruits and vegetables and abundant in antioxidants, nutrients, and other substances, reduced the risk of coronary heart disease and certain cancers. These initial promising results were not materialized by the more accurate and larger randomized controlled trials taking into account confounding factors.²⁷⁻³⁰

There are more than 54,000 dietary supplement products in the Natural Medicines Comprehensive Database (USA), of which only about 1/3 have some level of safety and effectiveness that is supported by scientific evidence. Consumer Reports magazine). Reuters 3/8/2010 [<http://www.reuters.com/article/us-usa-supplements-idUSTRE6721F520100803>].

By the mid 1990s, “antioxidant” became a household word and antioxidant-fortified dietary supplements and a large range of special foods and plants appeared on the market with incredibly superficial health benefits. According to the estimates of the Nutrition Business Journal report, the global nutrition and supplements market stood at US\$96 billion in 2012. A year later, it was approximately US\$104 billion globally. U.S.A market of dietary supplements was estimated in 2015 at US\$27.2 billion. China is also another important consumer in the market. With rising disposable incomes and increasing health awareness among the Chinese people, vitamins and dietary supplements are deemed a convenient choice for consumers looking to improve their health and wellbeing. In 2016 Chinese regulators released draft regulations governing nutritional supplements, a modest step toward modernizing the health food industry in one of the world’s largest economies. A proposal from China’s Food and Drug Administration (CFDA) would create a notification or recording system for the introduction of nutritional supplements, according to the U.S.-China Health Products Association (USCHPA), 2015 [<http://www.naturalproductsinsider.com/Articles/2015/01/China-Adopts-Proposed-Notification-System-for-Nut.aspx>].

Another trend in the last decades, which is characteristic of American consumers and people from Western developed countries (Canada, W. Europe, Australia), is that increasingly large numbers of middle class people became disenchanted with rising health care costs and the perceived impersonal nature of conventional “Western” medicine. In many countries there is a dramatic rise in the popularity of various complementary and alternative practices, including Chinese herbal medicine, Ayurvedic medicine (an Indian holistic medical system incorporating foods and herbs), acupuncture, and homeopathy. During the last decade the U.S. FDA and the EU attempted to increase regulation of herbal products and other botanicals and dietary supplements, as well as health labeling and list of contents, creating a platform of basic information among consumers and forcing dietary supplements manufacturers to follow hygiene practices and safety regulations. In the USA, the Dietary Supplement Health and Education Act (DSHEA) of 1994 classifies herbs as dietary supplements. In the EU countries the European Traditional Herbal Medicinal Products Directive (2004/24/EC) has provided a simplified registration scheme for traditional herbal medicinal products suitable for self-medication.³¹⁻³⁶

3. Dietary supplements global marketing with strong growth

Globally, the nutrition and supplements market stood at over US\$90 billion and in 2013 it was estimated at approximately US\$104 billion. The U.S.A market of dietary supplements was estimated in 2015 at US\$27.2 billion. Growth is expected to remain strong through the next years with expected increase between 5-6% per year. For comparison global sales of pharmaceuticals have reached a milestone of \$1 trillion in 2014 – and forecasts continued growth with the expectation of sales reaching \$1.3 trillion by 2018.³⁷⁻³⁹

Research analysis of various sections markets with large nutrition and dietary supplements industry show interesting sale numbers and growth projections. The global sports supplements market

in 2013 was worth US\$6.8 billion and growth 9%. These supplements include: whey, casein, egg white and soy proteins, amino acids, performance enhancers creatine, beta-alanine, D-ribose, Nitric oxide, testosterone, zinc and magnesium aspartate, green tea extracts for fat burning, raspberry ketones, caffeine, etc). The global fatty acids supplements (linoleic acid, eicosapentanoic , docosahexanoic, fish oil omega-3 fatty acids, flax seed oil, evening primrose oil, etc) market was estimated with value of US\$1.9 billion in 2013 and is expected to reach in 2020 value of 4.7 billion.^{38,39}

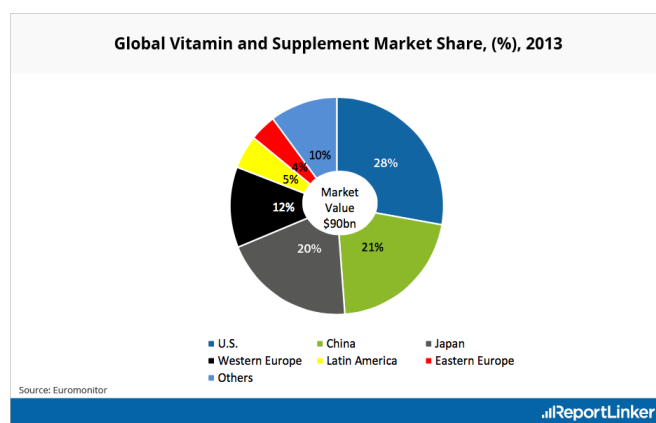


Figure 2. Global sales of dietary supplements are over US\$ 90- billion (source Euromonitor). The countries with the highest consumption rates are: USA 28%, China 21%, Japan, 20%, W. Europe 12%. ReportLinker [<http://www.reportlinker.com/ci02037/Vitamin-and-Supplement.html>]. The market is full of advertisements of nutritional supplements with excessive and controversial health claims.

The global mineral supplements market is increasing due to a growing geriatric population, increasing demand from pregnant women, and rising urban population. With the increasing population of baby boomers, spending on mineral supplements is anticipated to increase. The mineral supplements market are: macrominerals, calcium, phosphorous, zinc, alkaline pH booster, sodium, potassium, chlorine, sulfur, magnesium, and trace minerals: iron, boron, manganese, chromium, copper, iodine, cobalt, fluoride, selenium, colloidal silver. The global mineral supplements market was valued at \$9.9 million in 2014 and was expected to grow at 7.5% during the period 2015 - 2020.⁴⁰

Vitamin and polyvitamin supplements are very popular and their use as supplements, supported by increasing promotion adverts in growing every year. The global_vitamin supplements market, estimated to be valued at US\$37 billion in 2014, and is expected to grow at 6.5% during 2014 to 2020. This is mainly attributed to growing demand among consumer about preventative healthcare. Research on the vitamin supplement demand showed that is due to the increasing cost of healthcare, with people are turning towards vitamin supplements. Vitamin supplements included Vitamin C, E, B, A, beta-carotene, K, niacin, folic acid etc).⁴¹

The growing popularity and widespread use of internet has made finding health information and dietary supplements easier and faster. Although much of the information on the internet is valuable, at the same time it allows false and misleading information and advertisements with excessive therapeutics claims. Consumers may be misled by vendors' claims that herbal products can treat, prevent, diagnose, or cure specific diseases, despite regulations prohibiting such statements. Physicians should be aware of this widespread and easily accessible information. More effective regulation is required to put this class of therapeutics on the same evidence-based footing as other medicinal products.^{42,43} According to recent FDA testimony, dietary supplements, including vitamins, were consumed by 158 million Americans in the year 2000, that is more than 50% the US population.

Surveys showed that alternative medical therapies and herbal supplements were used by over 80 million people in the USA.^{44,45}

4. Concern among health professionals for the excessive use of dietary supplements

In the last decade national medical authorities, health professionals and nutritionists in developed countries became aware of the widespread and rapid increase of dietary supplements (DS) and excessive consumption by a wide range of the population. The global market is flooded with a variety of dietary supplements that have false therapeutic claims (difficult to test experimentally) and products which can be imported and distributed through the internet advertisements. Like drugs, dietary supplements have risks and side effects. But sellers aren't required to do research studies in people to prove that a dietary supplements are safe. And unlike drugs, DS are mostly self-prescribed with no input from informed medical sources like doctors, nurses, or pharmacists. Medical authorities agree that there's a lot of wrong information in the supplements market. Even for those who are usually well informed, it can be hard to find reliable information about the safe use and potential risks of DS.⁴⁶⁻⁴⁸

The most commonly reported reasons for using supplements were to "improve" or "maintain" overall health. Women used calcium products for "bone health" or for improving healthy skin appearance, whereas men were more likely to report supplement use for "heart health or to "lower cholesterol". Young people use supplements to enhance body function in sports. Older adults report motivations related to heart, bone and joint, and eye health. The consumption of DS is excessive in the USA with most Americans taking multivitamins. The primary reasons given for supplement use are for overall health and wellness or to fill nutrient gaps.^{49,50}

The concern of health professionals is that very little is known about the efficacy of DS for disease prevention and health needs. American scientists emphasize that randomized clinical trials are difficult because they tend to be short in duration, whereas many of the chronic diseases of public health concern have a long latency period (i.e., allergies, cancer, cardiovascular disease). Also, more investigations on the complex interplay of social, psychological, and economic determinants that motivate supplement choices are needed. At the same time the US FDA tracks reports of illness, injury, or reactions from dietary supplements. Recent FDA information of adverse or side effects shows that the number of reports has continued to climb each calendar year: 2010: 1,009 reports of DS for adverse health events to consumers, 2011: 2,047 reports and 2012: 2,844 reports. Exposures to supplements accounted for more than 100,000 calls to US poison control centers in 2013. Of these calls, more than 8,000 people were reportedly treated in health care facilities and 2 deaths reported to poison control centers.⁵¹ Emergency health departments in the USA between 2004-2013 received 23,000 emergency visits per year attributed to adverse health events related to DS consumption, with 2,154 cases needing hospitalization.⁵² Also, from 2012 to 2014 the FDA received 114 reports of adverse events (hepatitis outbreak, liver damage) involving consumers who ingested OxyELITEPro (promotes weight loss) supplements.⁵³

From 2007, some of the most well known scientists in the USA on nutrition, metabolism and epidemiology (professors Stampfer, Willett, Harvard, School of Public Health, and Bruce Ames and Joyce McCann, Nutrition and Metabolism Center, Children's Hospital Oakland Research Center) following a National Institutes of Health, reviewed the evidence on multivitamin/mineral (MVM) supplements and concluded that there was not sufficient evidence to recommend for or against for the prevention of chronic disease. Their bottom line was: "..... everyone would agree that all persons

should be encouraged to eat a good diet, but we are far from achieving this goal, especially among the poor. In most cases, a simple way to improve micronutrient status is to take an MVM. However, even if one eats an ideal diet and takes an MVM, some vitamins can remain below recommended concentrations in some groups...". "...The panel excluded this highly relevant body of evidence from consideration, and it came to the conclusion, "...The present evidence is insufficient to recommend either for or against the use of MVMs by the American public to prevent chronic disease". We contend that, by conveying the impression that long-term Randomized Controlled Trials (RCTs), which are inherently limited, represent the only scientific evidence relevant to "evidence-based decision making," the panel presents a highly biased and misleading picture...".⁵⁴

Many dietary supplements, even in the USA that has some of the most experienced health agencies, managed to escape the safety tests, labeling and regulations. The American agencies every year find toxic DS products in the US market that were finally recalled because they were found to contain banned toxic substances. Between 2009 and 2012, the FDA recalled 274 dietary supplements. The analysis of these DS were performed by GC-MS and found to contain toxic substances or additional pharmaceutical adulterants which were banned.^{55,56}

5. Scientific papers on the role of vitamin and mineral supplements in 2013

In the last decade the Randomized Control Trials (RCTs) of dietary supplements increased substantially in many developed countries. The results are mixed but the majority was negative for DS promoting health or preventing diseases. In 2013 three papers and an overall review of the results for the last decade on DS with the title "*Enough is enough. Stop wasting money on vitamin and mineral supplements*" were published in the prestigious and influential medical journal *Annals of Internal Medicine* in the USA.

In the first paper scientists reviewed in a systematic way all trial evidence (carried by the U.S. Preventive Services Task Force) for the recommendation on the efficacy of vitamin supplements for primary prevention for adults with no nutritional deficiencies. The review contained 3 trials of multivitamin supplements and 24 trials of single or paired vitamins that randomly assigned to more than 400,000 participants, the authors concluded that there was no clear evidence of a beneficial effect of supplements on all-cause mortality, cardiovascular disease, or cancer.⁵⁷

In the second paper, researchers evaluated the efficacy of a daily multivitamin to prevent cognitive decline among 5,947 men aged 65 years or older participating in the Physicians' Health Study II. After 12 years of follow-up, there were no differences between the multivitamin and placebo groups in overall cognitive performance or verbal memory.⁵⁸ These findings were compatible with a recent review of 12 fair- to good-quality trials that evaluated dietary supplements, including multivitamins, B vitamins, vitamins E and C, and omega-3 fatty acids, in persons with mild cognitive impairment or mild to moderate dementia. None of the supplements improved cognitive function.⁵⁹

In the third paper, Lamas and associates⁶⁰, assessed the potential benefits of a high-dose, 28-component multivitamin supplement in 1,708 men and women with a previous myocardial infarction participating in TACT (Trial to Assess Chelation Therapy). After a median follow-up of 4.6 years, there was no significant difference in recurrent cardiovascular events with multivitamins compared with placebo (hazard ratio, 0.89).⁶⁰

The supporting editorial in the same journal,⁶¹ added some previous highly relevant research papers, reviews and guidelines that have appraised the role of vitamin and mineral supplements in primary or secondary prevention of chronic disease but have consistently found null results or possible

harms.^{62,63} Evidence involving tens of thousands of people randomly assigned in many clinical trials shows that β -carotene, vitamin E, and possibly high doses of vitamin A supplements increase mortality and that other antioxidants, folic acid and B vitamins, and multivitamin supplements have no clear health benefit.^{62,64-66} Despite sobering evidence of no benefit or possible harm, use of multivitamin supplements increased among U.S. adults in the last decade (reaching over 30 billion in 2013). Similar trends have been observed in the United Kingdom and in other European countries.⁶⁷ The editorial concludes "...the message is simple conclude the scientists: Most supplements do not prevent chronic disease or death, their use is not justified, and they should be avoided...".

6. Arguments in support of dietary supplements and health benefits

After the publication of the scientific papers in *Annals of Internal Medicine* and the editorial "*Enough Is enough: Stop wasting money on vitamin and mineral supplements*" (2013) scientists of Oregon State University, Linus Pauling Institute (December 2013), an institute specializing on nutrition benefits of DS, carried a supporting note in their website for the balanced diet and prudent use of DS to fill the gap of useful micronutrients, vitamins and minerals for humans. Under the title "The case is far from closed for vitamins and mineral supplements".⁶⁸

"... While a well-balanced diet is the best way to get all of one's essential nutrients, the reality is that Americans don't get enough of them through diet alone. From the National Health and Nutrition Examination Survey (NHANES) we know that the large majority of the US population is not "well-nourished" and falls short of getting all of their vitamins and minerals from their diet in levels recommended." "... Studies have shown that people who take multivitamin/mineral (MVM) supplement with the recommended doses of the most vitamins and minerals can fill most of these nutritional gaps safely and at very low cost.^{69,70,71} Contrary to the impression that the authors (of the paper "enough is enough...") give in their editorial, the US population is inadequate in many vitamins and minerals, a result of the energy dense and nutrient-poor dietary pattern of Western populations, rather than over-consuming MVM and other DS. The known biological functions of vitamins and nutritionally-essential minerals are to maintain normal cell function, metabolism, growth and development, through their roles as essential cofactors in hundred of enzyme reactions and other biological processes-not to prevent or treat chronic disease. Nevertheless, the largest and longest randomized controlled trial (RCT) of MVM supplements conducted to date, the Physicians' Health Study II (PHS II), found a significant 8% reduction in total and epithelial cell cancer incidence in male physicians, and a 12% reduction in total cancer incidence excluding prostate cancer. The PHS II also found a significant 9% reduction in the incidence of total cataract. The findings are consistent with those of several other RCTs, and are even more impressive given the fact that the conventional RCT design is strongly biased against showing benefits of essential nutrients, in contrast to pharmaceutical drugs.⁷²⁻⁷⁷

Finally, the scientists of Linus Pauling Institute concluded "... Therefore, taking a daily MVM supplement will not only help fill the known nutritional gaps in the average American diet, thereby assuming normal biological function and metabolism and supporting good health, but may also have the added benefit of reducing cancer and cataract risk-which no existing pharmaceutical drug can do. To call "the case...closed" and label MVM supplements as useless, harmful or wasteful is highly premature and unscientific, and does not serve public health".

In the last few years numerous books and collections of scientific results were published or projected on websites of health agencies on dietary supplements, safety, cost, efficacy and health benefits vs risks.⁷⁸⁻⁸⁰

7. Recent scientific studies on vitamin and multivitamin supplements

Vitamin and multivitamin supplements in combination with calcium and antioxidants are the most widespread dietary supplements used by elderly people, pregnant women and people with disabilities for improving health, perinatal depression, improvement for neurologic and cognitive function, osteoporosis and progression of cancer. However, clinical trials on the use of vitamin supplements for promotion of health and prevention of disease have failed to demonstrate the strong associations seen in observational studies.

In Western countries (US and W. Europe) it is fairly common the consumption of multivitamins among the elderly to prevent disease and improve health. In the US half of adults report using one or more DS. Although epidemiologic evidence suggests that a diet rich in fruits and vegetables does have a protective effect on health, clinical trials on the use of vitamin supplements have failed to demonstrate their health or protective benefits.⁸¹

Other scientific data summarized in a recent review (29 clinical trials involving 24,300 women) do not support that routine vitamin C supplementation alone or in combination with other supplements for the prevention of fetal or neonatal death, poor fetal growth, preterm birth or pre-eclampsia. Additionally, further research is required to elucidate the possible role of vitamin C in the prevention of placental abruption and prelabour rupture of membranes.⁸²

A recent review examined 35 studies on diet, essential nutrients, and DS and their role in perinatal depression. The studies were grouped into four main categories based on the analysis of dietary intake: adherence to dietary patterns (9 studies); full panel of essential nutrients (6 studies); specific nutrients (including B vitamins, Vitamin D, calcium and zinc; 8 studies); and intake of fish PUFAs (12 studies). While 13 studies found no evidence of an association, 22 studies showed protective effects from healthy dietary patterns, multivitamin supplementation, fish and PUFA intake, calcium, Vitamin D, zinc and possibly selenium. Given the methodological limitations of existing studies and inconsistencies in findings across studies, the evidence on whether nutritional factors influence the risk of perinatal depression is still inconclusive.⁸³

Another randomized controlled trial (RCT) investigated the B-12 supplementation benefits on neurologic and cognitive function in moderately vitamin B-12-deficient people. Results of the RCT study did not support the hypothesis that the correction of moderate vitamin B-12 deficiency, in the absence of anemia and of neurologic and cognitive signs or symptoms, has beneficial effects on neurologic or cognitive function in later life.⁸⁴ Supplementation of vitamin B (folate, B₆ and B₁₂) has been investigated by a meta-analysis of 4 RCTs, for prevention or reduction in osteoporotic fracture and bone turnover. The results of this analysis failed to identify a risk-reducing effect of daily supplementation of B vitamins on osteoporotic fracture in patients with vascular disease and with relatively normal plasma Hcy (a blood test used to detect levels of homocysteine). In addition, the study did not find any positive effects of B vitamin supplementation on bone turnover.⁸⁵

Older adults in most countries use vitamin supplements (vitamins A, B, C, D and E) on the promise for health improvements and prevention of degenerative diseases (mortality, cancer, cardiovascular and cerebrovascular diseases, cataracts, age-related macular degeneration and bone diseases). The results of the most important studies on vitamins were summarized in a recent review. Data from studies demonstrate considerable variations, most confirming little to no benefit following supplementation in healthy adults. However, clear roles exist for vitamin supplementation in states of deficiency and in subgroups of older adults at high risk for deficiency of specific or multiple vitamins.⁸⁶

The prevention of cancer with vitamin supplements has been investigated extensively. Vitamin D is well known for its beneficial effects on health. A recent study included RCTs that compared vitamin D at any dose, duration, and route of administration versus placebo or no intervention in adults who were healthy or were recruited among the general population, or diagnosed with a specific disease. Vitamin D have been administered as supplemental vitamin D (vitamin D₃ (cholecalciferol) or vitamin D₂ (ergocalciferol), or an active form of vitamin D (1 α -hydroxyvitamin D (alfacalcidol), or 1,25-dihydroxyvitamin D (calcitriol)). Scientists concluded that, “ there is currently no firm evidence that vitamin D supplementation decreases or increases cancer occurrence in predominantly elderly community-dwelling women..”⁸⁷ Another recent review examined (from a systematic search of scientific literature) recent RCTs on the assessment of the effect of vitamin D supplementation on the prevention of childhood acute respiratory infections. The findings of the review indicated a lack of evidence supporting the routine use of vitamin D supplementation for the prevention of infections in healthy children; however, the findings suggested that such supplementation may benefit children previously diagnosed with asthma.⁸⁸

Prostate cancer is a very important cancer for men and increasing in the last decades due to diet of red meat, processed meat products and dietary fat. Long time ago it has been advocated that vitamin and selenium supplements might play a beneficial role for the prevention of prostate cancer. A recent review collected data from a PubMed search from 1990 to 2013. Results showed that dietary supplementation did not have any beneficial effects for the prevention of prostate cancer and indeed higher doses may be associated with a worse prognosis. There is no specific evidence regarding benefits of probiotics or prebiotics in prostate cancer.⁸⁹

Vitamin E supplementation and other vitamins have been advocated for positive benefits in pregnancy. A review collected 21 RCTs, involving 22,129 women, which assessed vitamin E in combination with vitamin C and/or other antioxidant agents. The data from these studies did not support routine vitamin E supplementation in combination with other supplements for the prevention of stillbirth, neonatal death, preterm birth, pre-eclampsia, preterm or term PROM or poor fetal growth.⁹⁰

8. Calcium, vitamin D, cardiovascular risk, osteoporosis, bone fractures, etc

Calcium (Ca) is an essential element in the human diet, but there is continuing controversy regarding its optimal intake, and its role in the pathogenesis of cardiovascular diseases, osteoporosis and bone fractures. Most studies show little evidence of a relationship between calcium intake and bone density, or the rate of bone loss. Very few food contain vitamin D. Synthesis of vitamin D occurs in the skin, after exposure to sun light (especially UV-B radiation), is the major natural source in humans.⁹¹ Vitamin D refers to a group of fat-soluble secosteroid compounds responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate, and zinc. In humans, the most important compounds in this group are vitamin D₃ (also known as cholecalciferol) and vitamin D₂ (ergocalciferol). A diet deficient in vitamin D in conjunction with inadequate sun exposure causes osteomalacia (or rickets in children). Dietary supplements containing Ca and vitamin D are widespread but there is a controversy regarding their optimal intake and their role in osteoporosis.⁹²

Studies demonstrated no relationship between dietary Ca intake and rate of bone loss over 5 years in healthy older women. A recent review analysed data from 5 recent large studies that have failed to demonstrate fracture prevention in their primary analyses. It was concluded that Ca supplements appear to have a negative risk-benefit effect, and so should not be used routinely in the prevention or treatment of osteoporosis.⁹³ In the other hand, if there deficiencies (Ca and vitamin D) in

older adults health professionals recommend as a cost-effective the daily supplementation with vitamin D to prevent or decrease the rate of osteoporotic fractures. A recent study concluded that the recommendation to use dairy products as the preferred source of calcium and vitamin D in aging males and females is supported by public health and health economic analyses.⁹⁴

A scientific meta-analysis investigated data from 9 trials in order to provide a quantitative assessment of the efficiency of intermittent, high dose vitamin D treatment on falls, fractures, and mortality among older adults. The high dose, intermittent vitamin D therapy did not decrease all-cause mortality among older adults. No benefit was seen in fracture or fall prevention. The risk ratio for hip fractures was 1.17 (95% Confidence Interval), while for non-vertebral fractures it was 1.06 and the risk ratio for falls was 1.02. All these results showed very small beneficial effects. Scientists concluded that supplementation of intermittent, high dose vitamin D may not be effective in preventing overall mortality, fractures, or falls among older adults.⁹⁵

The Women's Health Initiative for Calcium and vitamin D supplementation Study, was a 7 year, randomized, placebo controlled trial of calcium and vitamin D (1g calcium and 400 IU vitamin D daily) in 36,282 community dwelling postmenopausal women. The study followed the Incidence of four cardiovascular events and their combinations (myocardial infarction, coronary revascularisation, death from coronary heart disease, and stroke) assessed with patient-level data and trial-level data. In meta-analyses of placebo controlled trials of Ca or Ca and vitamin D data were available for 28,072 participants from 8 trials. In total 1,384 individuals had an incident myocardial infarction or stroke. Ca or combination of Ca and vitamin D increased the risk of myocardial infarction (relative risk 1.24) and the composite of myocardial infarction or stroke (1.15). Scientists concluded that Ca supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction.⁹⁶

9. Balanced diet and dietary supplements of omega-3 fatty acids

Omega-3 and omega-6 fatty acids (ω -3 & -6 FAs) are polyunsaturated fatty acids (PUFAs) considered to be important in human physiology. The most widely available dietary source of omega-3 FAs is oily fish, such as salmon, herring, mackerel, anchovies, menhaden, and sardines. Omega FAs have significant influence on the ratio and rate of production of eicosanoids, a group of hormones intimately involved in the body's inflammatory and homeostatic processes, which include the prostaglandins, leukotrienes, and thromboxanes. A recent trend has been to fortify food with omega-3 FAs supplements, such fortified bread, pizza, yogurt, orange juice, children's pasta, milk, eggs, confections, and infant formula to reduce mainly the risk for CVDs.

A review investigated a series of 11 studies for the association of dietary supplements of omega-3 fatty and risk to cardiovascular deaths with a total of 39,044 patients (after myocardial infarction, heart failure, peripheral vascular disease, etc) The average dose of EPA/DHA (fish oil containing EicosaPentaenoic Acid/ DocosaHexaenoic Acid) was 1.8 g/day and the mean duration of follow-up was 2.2 years. Dietary supplementation with omega-3 fatty acids significantly reduced the risk of cardiovascular deaths at 0.87, sudden cardiac death 0.87, all-cause mortality 0.92, and nonfatal cardiovascular events 0.92. The mortality benefit was largely due to the studies which enrolled high risk patients. Meta-regression failed to demonstrate a relationship between the daily dose of omega-3 fatty acid and clinical outcome. The scientists concluded that dietary supplementation with omega-3 fatty acids should be considered in the secondary prevention of cardiovascular events.⁹⁷

A systematic review explored more than 15,000 articles in the scientific literature, including 48 randomized control trials (with 36,913 participants) and 41 epidemiological cohort studies that focused

on health benefits and risks from diets with additional omega-3 (ω -3) fatty acids. The health effects were concerned with cardiovascular diseases, general mortality and malignant neoplasms. The pooled estimate showed no strong evidence of reduced risk of total mortality (relative risk 0.87) or combined cardiovascular events (0.95) in participants taking additional omega-3 fatty acids. Scientists concluded that long chain and shorter chain omega-3 fatty acids do not have a clear effect on total mortality, combined cardiovascular events, or cancer.⁹⁸

Many studies in the last decade showed that long-chain omega-3 polyunsaturated fatty acids (PUFAs) or omega-3 PUFAs are able to modulate inflammation, hyperlipidemia, platelet aggregation, and hypertension, under different mechanisms for conditioning cell membrane function and composition eicosanoid production, and gene expression. A review in 2014 analyzed the influence of omega-3 PUFAs status and intake on brain function, cardiovascular system, immune function, muscle performance and bone health in older adults. It was found that omega-3 fatty acids can have benefits in reducing the risk of cognitive decline in older people, but more studies are needed to confirm the role of omega-3 (ω -3) in maintaining bone health and preventing the loss of muscle mass and function associated with ageing.⁹⁹

Osteoporosis is a global health problem that leads to an increased incidence of fragility fracture. In the last decade there is medical recommendation of higher fish oil diet intakes. Findings from human bone cell culture experiments have revealed both benefits and detriments to bone-related outcomes depending on the quantity and source of PUFAs. Observational and randomized controlled trials (RCTs) have produced enough data to suggest that higher fatty fish intake is strongly linked with reduced risk of fragility fracture. Human studies largely support that a greater intake of total PUFAs, total n-6 (ω -6 FAs) fatty acid, and total n-3 (ω -3) fatty acid, contributed for higher bone mineral density and reduced risk of fragility fracture.¹⁰⁰ Also, omega fatty acids in combination with other antioxidants, such as resveratrol, can have a major therapeutic role. A recent review collected some of the key studies involving the health benefits supported by a combination of resveratrol and ω -3 FAs intake. Many studies showed that resveratrol, as a potent antioxidant reduces oxidative stress in endoplasmic reticulum, and proved to have a significantly protective role in most important pathophysiological factors associated with CVD conditions. Numerous research projects demonstrated the reduction of the risk of coronary heart disease, hypertension, and stroke, by a combination of resveratrol and ω -3 fatty acids derived from fish oils.¹⁰¹

Many studies support the notion that omega-3 fatty acids are essential for a balanced human diet, and a certain amount of omega-3 is needed in human daily diet. Currently, there is increasing evidence of the benefits of omega-3 by different medical professional bodies with the stronger evidence for cardiovascular disease (CVDs). There is a broad consensus among scientists that fish and seafood are the optimal sources of n-3 FAs and consumption of approximately 2-3 servings per week is recommended for good health. But it has been noted that the scientific evidence of benefits from n-3 FAs supplementation has diminished over time, probably due to a general increase in seafood consumption in developed countries, better pharmacological intervention and acute treatment of patients with CVD diseases.¹⁰²⁻¹⁰⁴

10. Dietary zinc, iron and selenium supplementation, health benefits/risks

Zinc is essential trace element for normal biological growth, reproduction and immune function. In addition, Zn is vital for the functionality of more than 300 enzymes, for the stabilization of DNA, and for gene expression. Zinc deficiency is estimated to be responsible for 4% of global child morbidity and

mortality. The adult human contains 2–3 g of zinc (Zn). Conservative estimates suggest that around 25% of the world's population is at risk of zinc deficiency.¹⁰⁵ Most of the affected are poor, and rarely consume foods rich in highly bioavailable zinc, while subsisting on foods that are rich in inhibitors of zinc absorption and/or contain relatively small amounts of bioavailable zinc. Food choice is a major factor affecting risk of zinc deficiency. A major challenge that has not been resolved for maximum health benefit is the proximity of the recommended dietary allowance (RDA) and the reference dose (RfD) for safe intake of zinc. The current assumed range between safe and unsafe intakes of zinc is relatively narrow.¹⁰⁶

A recent review included data from 21 randomized controlled trials (RCTs) reported in 54 papers involving over 17,000 women and their babies. The results showed that there was a 14% relative reduction in preterm birth for zinc compared with placebo. These results appeared in primarily in trials involving women of low income and this has some relevance in areas of high perinatal mortality. There was no convincing evidence that Zn supplementation during pregnancy resulted in other useful and important health benefits. According to the scientists these results reflected poor nutrition in impoverished areas and the need for a balanced diet than dietary Zn supplements.¹⁰⁷

Scientists experimented with Zinc supplementation that may remodel the immune alterations in elderly leading to healthy ageing. Several zinc trials have been carried out with contradictory data, perhaps due to incorrect choice of an effective zinc supplementation in old subjects showing subsequent zinc toxic effects on immunity. Old subjects with specific IL-6 polymorphism were more prone for zinc supplementation than the entire old population, in whom correct dietary habits with foods containing zinc (Mediterranean diet) may be sufficient in restoring zinc deficiency and impaired immune response.¹⁰⁸

It is well known that Zinc (Zn) and Iron (Fe) are essential minerals often present in similar food sources. A review analysed the current medical and nutritional literature on Zn and Fe supplementation and its impact on mood or cognition in pre-menopausal women. 10 RCTs and one non-randomized controlled trial were found to meet the inclusion criteria. The results showed that 7 studies found improvements in aspects of mood and cognition after iron supplementation. Iron supplementation appeared to improve memory and intellectual ability in participants aged between 12 and 55 years of age regardless of whether the participant was initially iron insufficient or iron-deficient with anaemia. Also, 3 RCTs provided evidence to suggest a role for Zn supplementation as a treatment for depressive symptoms. Overall, the current scientific literature indicated a positive effect of improving Zn status on enhanced cognitive and emotional functioning. However, further study involving well-designed randomized controlled trials is needed to identify the impact of improving iron and zinc status on mood and cognition.¹⁰⁹

Many children in developing countries have inadequate zinc nutrition. It has been shown that zinc supplementation reduces the risk of respiratory infections and diarrhea, the two leading causes of morbidity and mortality in young children worldwide. In childhood diarrhea oral zinc also reduces illness duration. Oral Zn is therefore recommended for the treatment of acute diarrhea in young children. An updated review showed that the results from the studies that have measured the therapeutic effect of zinc on acute respiratory infections, however, are conflicting. Also, the results of therapeutic Zn for childhood malaria are so far not promising.¹¹⁰

Selenium is another very important trace element (micronutrient) incorporated into selenoproteins that have a wide range of pleiotropic effects, ranging from antioxidant and anti-inflammatory effects to the production of active thyroid hormone. In the past 10 years, the discovery of disease-associated polymorphisms in selenoprotein genes has drawn attention to the relevance of selenoproteins to health. Low selenium status has been associated with increased risk of mortality, poor

immune function, and cognitive decline. Higher selenium status or selenium supplementation has antiviral effects, is essential for successful male and female reproduction, and reduces the risk of autoimmune thyroid disease. Prospective studies have generally shown some benefit of higher selenium status on the risk of prostate, lung, colorectal, and bladder cancers, but findings from trials have been mixed, which probably emphasises the fact that supplementation will confer benefit only if intake of a nutrient is inadequate. Supplementation of people who already have adequate intake with additional selenium might increase their risk of type-2 diabetes. The crucial factor that needs to be emphasised with regard to the health effects of selenium is the inextricable U-shaped link with status; whereas additional selenium intake may benefit people with low status, those with adequate-to-high status might be affected adversely and should not take selenium supplements.¹¹¹

Selenium supplementation and cancer has been investigated by various epidemiological studies. A recent extensive review analysed data from 55 prospective observational studies (including more than 1,100,000 participants) and 8 RCTs (with a total of 44,743 participants). Although an inverse association between selenium exposure and the risk of some types of cancer was found in some observational studies, this cannot be taken as evidence of a causal relation, and these results should be interpreted with caution. These studies have many limitations, including issues with assessment of exposure to selenium and to its various chemical forms, heterogeneity, confounding and other biases. Conflicting results including inverse, null and direct associations have been reported for some cancer types. RCT studies have yielded inconsistent results, although the most recent studies, characterized by a low risk of bias, found no beneficial effect on cancer risk, more specifically on risk of prostate cancer. Some RCTs suggested harmful effects of selenium exposure. The reviewers concluded that there is no convincing evidence that selenium supplements can prevent cancer in humans.¹¹²

Iron deficiency anemia in humans is an important public health issue, especially for infants, children, and women with menorrhagia. Oral iron supplements are the cheapest, safest, and most effective treatment. A retrospective study collected for two years 41 patients with iron deficiency anemia who continuously took oral ferric for over one month and then switched to oral ferrous due to poor therapeutic effects. The results showed that the mean blood test values for all patients significantly increased after switching to ferrous iron. This study found that blood test values improved after iron deficiency anemia female patients who displayed poor therapeutic effects with oral ferric switched to ferrous. A literature review in the same study showed that the risk for gastrointestinal problems with ferrous is higher than that with ferric.¹¹³

Randomised Control Trials or quasi-randomised trials evaluating the effects of oral preventive supplementation with daily iron, iron + folic acid or iron + other vitamins and minerals during pregnancy. The study concluded that iron supplementation reduces the risk of maternal anaemia and iron deficiency in pregnancy but the positive effect on other maternal and infant outcomes is less clear. Implementation of iron supplementation recommendations may produce heterogeneous results depending on the populations' background risk for low birthweight and anaemia, as well as the level of adherence to the intervention.¹¹⁴

Recent studies showed that intermittent iron supplementation is a promising strategy in reducing iron deficiency and iron deficiency anaemia. Also, a small number of studies investigated the effect of iron interventions on developmental outcomes, such as growth and cognition, and provided mixed results. Some studies reported that iron intervention increased morbidity and caused unfavourable shifts in the gut microbial composition along with increases in intestinal inflammation, particularly in children with a high infectious disease burden. Scientists suggested that there is a need for studies in children from low and middle-income populations to provide evidence for the

beneficial effects of iron interventions on functional outcomes (iron deficiency and anaemia), and to explore potential mechanisms underlying the negative effects of iron reported in recent trials.¹¹⁵

11. Dietary phytochemicals, herbs, loss of weight and supplements

The global market of Dietary Supplements (DS) is full of numerous “natural” therapies with incredulous claims and very little evidence of health benefits. Dietary supplements involving flavonoids, polyphenols, herbal therapies (Ginkgo, ginseng, Echinacea, etc), and for reduction of body weight (chitosan, picolinate, *Ephedra sinica*, *Garcinia cambogia*, etc) are claiming beneficial biological effects without risk of adverse effects.

But the scientific evidence is very different. Numerous studies have shown that although consumption of dietary phytochemicals such as flavonoids has been suggested to have beneficial biological effects including the prevention of cancer and heart disease, there is considerable evidence to suggest that such compounds are not without risk of adverse effects. The risk of adverse effects is likely increased by the use of pharmacological doses in prevention/treatment and supplement situations and genetic polymorphisms or drug-drug interactions that increase the bioavailability of test compounds.¹¹⁶

The DS market is full of popular herbal remedies. Scientific studies investigated the efficacy and safety of ginkgo, St. John's wort, ginseng, echinacea, saw palmetto, and kava. The safety assessments were based on systematic reviews of RCTs. Although data supported the efficacy of some of these popular herbal medicinal products, the published evidence suggests that ginkgo is of questionable use for memory loss and tinnitus but has some effect on dementia and intermittent claudication. St. John's wort was efficacious for mild to moderate depression, but serious concerns exist about its interactions with several conventional drugs. Well-conducted clinical trials do not support the efficacy of ginseng to treat any condition. Echinacea may be helpful in the treatment or prevention of upper respiratory tract infections, but trial data are not fully convincing. Saw palmetto has been shown in short-term trials to be efficacious in reducing the symptoms of benign prostatic hyperplasia. Kava is an efficacious short-term treatment for anxiety. Studies showed that none of these herbal medicines were free of adverse effects. Because the evidence is incomplete, risk-benefit assessments are not completely reliable, and much knowledge is still lacking.¹¹⁷

Numerous supplements are used in the global market for body weight reduction without evidence of effective effects and some of them containing risks. An overall critical review assessed the efficacy by using 5 systematic reviews and meta-analyses and 25 additional trials. Data on the following dietary supplements were identified: chitosan, chromium picolinate, *Ephedra sinica*, *Garcinia cambogia*, glucomannan, guar gum, hydroxy-methylbutyrate, plantago psyllium, pyruvate, yerba maté, and yohimbe. The reviewers identified some encouraging data but no evidence beyond a reasonable doubt that any specific DS was effective for reducing body weight. The only exceptions were for *E. sinica*– and ephedrine-containing supplements, which have been associated with an increased risk of adverse events. Reviewers concluded that the evidence for most DS as aids in reducing body weight was not convincing. None of the reviewed DS can be recommended for over-the-counter use.¹¹⁸

A large study involving 124 086 men and women [Health Professionals Follow-up Study (HPFS), Nurses' Health Study (NHS), and Nurses' Health Study II (NHS II)] measured self reported change in weight over multiple four year time intervals between 1986 and 2011. Results showed that Increased consumption of most flavonoid (flavonols, flavan-3-ols, anthocyanins, flavonoid polymers) was inversely associated with weight change over four year time intervals, after adjustment for simultaneous changes in other lifestyle factors including other aspects of diet, smoking status, and physical activity.

Scientists concluded that intake of food rich in flavonoids may contribute to weight maintenance in adulthood and prevent obesity.¹¹⁹

The use of herbal or alternative medicine as therapeutic supplements for neuropathy diseases has garnered rising interest in recent years. The Internet is a ubiquitous source of information/market for these supplements. A study investigated 184 websites, 28% claimed to decrease CKD (chronic kidney diseases) progression, 60% did not advise to consult a doctor before taking the supplement, and >90% did not mention any potential drug interaction, disease interaction, or caution in use during pregnancy or in children. Scientists concluded that nephrologists need to be cognizant of the lack of substantiated proven benefits of these substances (in internet sites) and of the potential adverse effects in the animal models that can translate to the patients. Regulation of these products must change to prevent patient harm and misinformation.¹²⁰

12. Dietary supplements and prevention of cancer

Dietary supplements are widely used among patients with cancer who perceive them to have strong anticancer and antioxidant properties. Large-scale, randomized cancer prevention trials have mainly been negative, with some notable adverse and beneficial effects. These trials showed that β -carotene increased the risk of lung and stomach cancer, vitamin E increased prostate cancer and colorectal adenoma, and selenium reduced gastric and lung cancer in populations with low selenium levels but increased rates in those with higher levels. Both β -carotene and vitamin E supplementation increase overall mortality. A recent review examined phase II and III trials that investigated the effects of multivitamins, antioxidants, vitamin D, and n-3 supplements on outcome and toxicity from cancer treatments. Although vitamin E and β -carotene reduced toxicity from radiotherapy among patients with head and neck cancer, it has been found to increase recurrence, especially among smokers. Antioxidants have mixed effects on chemotherapy toxicity, but there are no data on outcome. Vitamin D deficiency is relatively common among patients with cancer, and ongoing phase III trials are studying the effect of vitamin D on outcome as well as optimum vitamin D and calcium intakes for bone health. Docosahexanoic and eicosapentanoic acid supplements have mixed effects on cachexia and are currently being tested as potential adjuncts to maximize response to chemotherapy. Dietary supplementation tailored to an individual's background diet, genetics, tumor histology, and treatments may yield benefits in subsets of patients.^{121,122}

In the last decade numerous studies investigated the anticancer properties for Resveratrol (antioxidant polyphenol in red wine). Studies in experimental animals showed that resveratrol can protect against angiogenesis, inflammation, and cancer, but dietary sources of resveratrol are not enough to have an impact on health. Pre-clinical findings have provided mounting evidence that resveratrol may confer health benefits and protect against a variety of medical conditions and cancer, but there is no consistent evidence. Most of the studies that have investigated the effect of resveratrol administration on patient outcomes have been limited by their sample sizes for diseases, such as cancer, diabetes, neurodegeneration, CVDs and other age-related ailments. There is an open question as to resveratrol supplementation for therapeutic anticancer benefits, especially for prostate.¹²³ The relationship between dietary polyphenols and the prevention of prostate cancer has been examined by a great number of clinical trials. Although results are sometimes inconsistent and variable, there is a general agreement that polyphenols hold great promise as chemopreventive agents for the future management of prostate cancer, including resveratrol. Dietary supplements of polyphenols can act as key modulators of signaling pathways and affect post-translational modifications and microRNA expressions.¹²⁴

Dietary supplementation for cancer prevention or for therapeutic intervention (market claims not consistent with supplements) has become a multibillion-dollar industry all over the world. There is a widespread belief that nutritional supplements can ward off chronic disease, including cancer, although there is little to no scientific evidence. To the contrary, there is now evidence that high doses of some supplements increase cancer risk. Despite this evidence, marketing claims by the supplement industry continue to imply anticancer benefits. Scientists and medical professionals agree that insufficient government regulation of the marketing of DS products resulted in unsound advice to cancer patients and consumers. According to the most recent National Health and Nutrition Examination Survey (2003–2006), 50% of the US adult population uses one or more dietary supplements; most of those are multivitamin and/or multimineral supplements despite the results of observational studies that provide little evidence that multivitamins reduce cancer risk, and there have been no randomized studies of multivitamins for cancer prevention.¹²⁵

13. Conclusion

Scientists and health professionals agree that dietary supplements (DS) can be under certain conditions beneficial to human health, but should not replace complete and balanced daily meals of foods. For the last decades informed medical agencies, doctors, pharmacists and nutritionists inform the consumers that there's a lot of wrong information in the global supplements market. Many DS even in developed countries managed to escape the safety tests, labeling and health regulations. Scientists in the USA and Western Europe specializing on nutrition, metabolism and epidemiology reviewed the evidence for DS supplements and concluded that there was not sufficient evidence to recommend for or against for the prevention of chronic disease. Results from Randomized Control Trials of DS showed that the majority are negative for health benefits or for preventing diseases. Self-prescription of DS should be avoided and patients, older people, pregnant women, young and people with disabilities should be informed and advised by their doctors or pharmacists for dietary supplementation.

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ΦΑΡΜΑΚΕΥΤΙΚΗ, 28, Π:69-92, 2016

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PHARMAKEFTIKI, 28, Π:69-92, 2016 ΑΡΘΡΟ ΕΠΙΣΚΟΠΗΣΗΣ/ REVIEW ARTICLE

Διατροφικά Συμπληρώματα: Ωφέλιμα στην Υγεία του Ανθρώπου ή Απλώς Εφησυχασμός της Σκέψης; Κριτική επισκόπηση για την διαμάχη ωφέλειας/κινδύνου στα διατροφικά συμπληρώματα

Περίληψη

Διατροφικά συμπληρώματα (ΔΣ) είναι βιταμίνες, μεταλλικά ιόντα, πρόσθετες χημικές ουσίες, φυτά και βότανα που προστίθενται στα τρόφιμα ή καταναλώνονται με διάφορους τρόπους για να βελτιώσουν την ανθρώπινη υγεία. Επίσης, διατροφικά συμπληρώματα χρησιμοποιούνται από άτομα για να δυναμώσουν τον ανθρώπινο οργανισμό τους ή για να περάσουν μια δύσκολη περίοδο της ζωής τους. Επιστήμονες, ιατρικές υπηρεσίες και διατροφολόγοι συμφωνούν ότι ορισμένα διατροφικά συμπληρώματα κάτω από ορισμένες συνθήκες είναι ωφέλιμα στην ανθρώπινη υγεία, αλλά δεν μπορούν να αντικαταστήσουν πλήρη και ισορροπημένη καθημερινή διατροφή με όλα τα απαραίτητα συστατικά. Η πλέον έγκυρη υπηρεσία των ΗΠΑ, η Food and Drug Administration (FDA) υπογραμμίζει ότι «... σε αντίθεση με τα φάρμακα, τα διατροφικά συμπληρώματα δεν μπορούν να πραγματοποιήσουν πρόληψη, να διαγνώσουν, να αναστείλουν ή να θεραπεύσουν ασθένειες. Τα ΔΣ δεν επιτρέπεται να προβάλλουν ή να διεκδικούν ιδιότητες ότι περιορίζουν τον πόνο ή ότι θεραπεύουν καρδιακές ασθένειες, κλπ...». Η παγκόσμια αγορά των διατροφικών συμπληρωμάτων είναι τεράστια και υπολογίζεται ότι ξεπέρασε τα 90 δισεκατομμύρια δολάρια (US\$) το 2013. Η χώρα με την μεγαλύτερη αγορά ΔΣ είναι οι ΗΠΑ με αγορά άνω των 30 \$ δισεκατομμυρίων ετησίως. Για πολλά χρόνια οι γιατροί, νοσηλευτές, φαρμακοποιοί και διατροφολόγοι γνωρίζουν ότι πολλά από τα ΔΣ που κυκλοφορούν στην αγορά ισχυρίζονται για υπερβολικές θεραπευτικές ιδιότητες, εσφαλμένες διεργασίες χωρίς ιατρικά πειραματικά δεδομένα, ενώ

σε πολλές χώρες όπως και στις ΗΠΑ εκατοντάδες προϊόντα έχουν αποφύγει τον φαρμακευτικό έλεγχο και τους κανονισμούς των υγιεινών προδιαγραφών που είναι απαραίτητοι στα φάρμακα και τρόφιμα. Από το 2007, μερικοί από τους πιο γνωστούς επιστήμονες στις ΗΠΑ, οι οποίοι εξειδικεύονται στην διατροφή, μεταβολικές διεργασίες στον ανθρώπινο οργανισμό και ιατρική επιδημιολογία πραγματοποίησαν εκτεταμένες και πολύχρονες έρευνες για πολυβιταμινούχα συμπληρώματα, μεταλλικά ιόντα και διάφορα ΔΣ που έχουν μεγάλη κυκλοφορία στην αγορά. Τα αποτελέσματα των ερευνών αυτών δείχνουν, κατά πλειοψηφία, ότι τα ΔΣ δεν έχουν ωφέλιμες δράσεις ή θεραπευτικές ιδιότητες αλλά και σε ορισμένες περιπτώσεις αρνητικές επιπτώσεις στην υγεία των καταναλωτών. Οι Τυχαίοποιημένες Ελεγχόμενες Δοκιμές (ΤΕΔ) (Randomized Control Trials, RCTs) είναι εξειδικευμένες έρευνες στις οποίες συμμετέχουν η ομάδα placebo (εικονικό φάρμακο) και η ομάδα ελέγχου και γίνεται τυχαίοποιημένη έρευνα για συγκριτικά θετικές ή αρνητικές επιπτώσεις μετά από ορισμένο χρονικό διάστημα με διατροφή ενισχυμένη με ΔΣ. Την τελευταία δεκαετία έχουν διεξαχθεί πολλές επιδημιολογικές και ΤΕΔ έρευνες και τα αποτελέσματα έχουν παρουσιασθεί στην επιστημονική βιβλιογραφία σε γνωστά έγκυρα ιατρικά περιοδικά. Τα αποτελέσματα ήταν στην πλειοψηφία τους αρνητικά. Το 2013 παρουσιάσθηκαν τα οριστικά συμπεράσματα πολλών ΤΕΔ σε 3 επισκοπήσεις και ένα άρθρο κριτική των συμπερασμάτων στο έγκυρο ιατρικό περιοδικό *Annals of Internal Medicine* με τον τίτλο «...μέχρις εδώ..σταματήστε να ξοδεύετε τα χρήματά σας σε βιταμίνες και άλλα διατροφικά συμπληρώματα...». Τα άρθρα αυτά είχαν σοβαρή επίδραση στον ιατρικό κόσμο πολλών ανεπτυγμένων χωρών και πολυάριθμες νεότερες έρευνες επιβεβαίωσαν τα προηγούμενα αποτελέσματα ή περιορισμένη ωφέλιμη δράση για την υγεία. Η επισκόπηση αυτή περιλαμβάνει σημαντικά στοιχεία για την αγορά των διατροφικών συμπληρωμάτων, στατιστικά δεδομένα και γενικές ιατρικές έρευνες. Επίσης, η επισκόπηση περιλαμβάνει μεγάλο αριθμό επιλεγμένων επιστημονικών μελετών από έγκυρα ιατρικά περιοδικά για επιδημιολογικές και ΤΕΔ έρευνες, από διάφορες χώρες για μεγάλη ποικιλία ΔΣ με αρνητικά και θετικά αποτελέσματα καθώς και κριτική παρουσίαση των αποτελεσμάτων. Καλύπτει μεγάλο αριθμό των πλέον γνωστών και εμπορικά επιτυχημένων διατροφικών συμπληρωμάτων που χρησιμοποιούνται από ηλικιωμένους, αθλητές, έγκυες γυναίκες και νέα άτομα.

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ΛΕΞΕΙΣ-ΚΛΕΙΔΙΑ : Διατροφικά Συμπληρώματα, Ισορροπημένη Διατροφή, Βιταμίνες, Ιχνοστοιχεία, Τυχαίοποιημένες Ελεγχόμενες Δοκιμές, Ωφέλεια στην Υγεία, Διεθνής Αγορά Διατροφικών Συμπληρωμάτων

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References (Βιβλιογραφία)

1. Hollenstein J. *Understanding Dietary Supplements*. Pri-Med Institute, Boston, MA, 1994.
2. Mason P. *Dietary Supplements*. (4th edition). Pharmaceutical Press, London, 2011.
3. Watson RR, Gerald JK, Prredy VR (Eds). *Nutrients, Dietary Supplements, and Nutraceuticals. Cost Analysis versus Clinical Benefits*. Springer Science & Business Media, Berlin, 2011.
4. Cupp MJ, Tracy TS (Eds). *Dietary Supplements. Toxicology and Clinical Pharmacology*. Humana Press, New York, 2003.
5. Begins K, Kreft S (Eds). *Dietary Supplements. Safety, Efficacy and Quality*. Woodhead Publishing (inprint of Elsevier), Amsterdam, 2014.
6. National Institutes of Health, USA. Diet Supplements: What you need to know [https://ods.od.nih.gov/HealthInformation/DS_WhatYouNeedToKnow.aspx].
7. Coppens P, da Silva MF, Pettman S. European regulations on nutraceuticals, dietary supplements and functional foods: A framework based on safety. *Toxicology* 221(1):59-74, 2006.
8. National Organization of Medicines (Εθνικός Οργανισμός Φαρμάκων, ΕΟΦ). Particular Nutrition Food, Food Supplement and Biocides Assessment Section, National Organization of Medicines, 284 Mesogeion Av., Holargos, Athens, Greece [relation@eof.gr].
9. Germany. Bundesministerium für Ernährung, Landwirtschaft und Verbraucherschutz (BMELV) Federal Ministry of Food, Agriculture and Consumer Protection, Rochusstr. 1 D-53123 Bonn.
10. Food Standards Agency, UK. Trade Information Sheet No. 7. Food/Dietary Supplements and Health Foods. November 2015. [<http://www.food.gov.uk/sites/default/files/trade-info07.pdf>].
11. Chemical Inspection and Regulation Service (CIRS). 12 Significant Changes of China Dietary Supplement Regulation System, 11 August 2015 original article from CIRS [<http://www.cirs-reach.com/news-and-articles/12-significant-changes-of-china-dietary-supplement-regulation-system.html>]. Hangzhou, China.
12. Japan, Ministry of Health and Welfare. Food Safety Commission, Consumer Affairs Agency, Chronology of Regulations/Guidelines on Nutrition and Health Claims in Japan, 1991. Foods for Specified Health Use (FOSHU), 1995. Nutrition Labeling Standards 1997-2001. Foods with Nutrient Function Claims (FNFC), 2003. Food Safety Commission, 2005. Consumer Affairs Agency [<http://www.sideshare.net/Adrienna/japan-regulations-guidelines-for-functionnal-foods>].
13. Price S. Understanding the importance to health of a balanced diet. *Nursing Times* 101(1):30-31, 2005.

14. Katz DL, Meller S. Can we say what diet is best for health? *Ann Rev Public Health* 35, 83-103, 2014.
15. Widmer RJ, Flammer AJ, Lerman LO, Lerman A. The Mediterranean diet, its components, and cardiovascular disease. *Am J Medicine* 128(3), 229-238, 2015.
16. ... WHO. Global Strategy on Diet, physical activity and health, WHO publications-reports, Geneva, <http://www.who.int/dietphysicalactivity/diet/en/>]
17. WHO/FAO. Release Independent Expert Report on Diet and Chronic Disease, Geneva, 2003 .. [<http://www.who.int/mediacentre/news/releases/2003/pr20/en/>].
18. Shils ME, Shike M, Ross AC, Caballero B, Cousins RJ. *Modern Nutrition in Health and Disease*. (10th edition), Lippincott Williams & Wilkins, Wolters Kluwer, Philadelphia, 2006.
19. Fraga CG (Ed). *Plant Phenols and Human Health. Biochemistry, Nutrition, and Pharmacology*. Wiley & Sons, Hoboken, NJ, 2010.
20. Brody T. *Nutritional Biochemistry*. Academic Press (inprint of Elsevier), Amsterdam, Boston, 1999 (2nd ed).
21. Pauling L: *Vitamin C and the Common Cold*. WH Freeman, San Francisco, 1976.
22. Cameron E, Pauling L. Supplemental ascorbate in the supportive treatment of cancer: reevaluation of prolongation of survival times in terminal human cancer. *Proc Natl Acad Sci USA* 75:4538-4542, 1978.
23. Creagan ET, Moertel CG. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. *N Engl J Med* 301, 687-690, 1979.
24. Tschetter L, Creagan ET, O'Fallon JR, Schutt AJ, et al. A community-based study of vitamin C (ascorbic acid) in patients with advanced cancer. *Proc Am Soc Clin Oncol* 2, 92, 1983.
25. Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, et al. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. *N Engl J Med* 312, 137-141, 1985.
26. Heaney ML, Gardner JR, Karasavvas N, Golde DW, Scheinberg DA, Smith EA, et al. Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. *Cancer Res* 68:8031-8038, 2008.
27. Liu RH. Health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. *Am J Clin Nutr* 78(3), 5175-5205, 2003.
28. Gaziano JM, Glynn RJ, Christen WC, et al. Vitamins E and C in the prevention of prostate and total cancer in men The Physicians' Health Study II Randomized Controlled Trial. *JAMA* 301(1), 52-62, 2009.
29. Leanders M, Leufkens AM, Siersema PD, van Duijnhoven FJB, Vrieling A, et al. Plasma and dietary carotenoids and vitamins A, C and E and risk of colon and rectal cancer in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 135(12), 2930-2939, 2014.
30. Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP, et al. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: An updated systematic evidence review for the U.S. Preventive Services Task Force FREE. *Annls Intern Med* 159(12), 824-834, 2013.
31. WHO. *National Policy on Traditional Medicine and Regulation of Herbal Medicines - Report WHO Global Survey* (2005; 168 pp) [<http://apps.who.int/medicinedocs/pdf/s7916e/s7916e.pdf>].
32. De Smet PAGM. Herbal medicine in Europe. Relaxing regulatory standards. *N Engl J Med* 352, 1176-1178, 2003.
33. Fermer RE. Regulating herbal medicine in the UK. *Br J Med* 333: 62-63, 2005.
34. Valavanidis A. Herbs and traditional therapeutic plants. *Scientific American* (Greek Edition), April 2006, 92-95, 2006 (in Greek).
35. Bent S. Herbal Medicine in the United States: Review of Efficacy, Safety, and Regulation. *J Gen Intern Med* 23(6), 854-859, 2008.
36. Walker DR. *Report on the Regulation of Herbal Medicine and Practitioners*. Dpt of Health and the Medicines (UK), Healthcare Products Regulatory Agency, 26 March, 2015. . [http://www.dcsceience.net/Report_on_Regulation_of_Herbal_Medicines_and_Practitioners.pdf]
37. McKinsey & Company. Consumer and Shopping Insights. Cashing in on the booming market for dietary supplements. Dec. 2013 [https://www.mckinseyonmarketingandsales.com/sites/default/files/pdf/CSI_VMHS_FNL_0.pdf] (accessed February 2016).
38. Nasdag. Globe News Wire. Global Nutrition and Supplements Market: History, Industry Growth, and Future Trends by PMR, New York, Jan 2015. [<https://globenewswire.com/news-release/2015/01/27/700276/10117198/en/Global-Nutrition-and-Supplements-Market-History-Industry-Growth-and-Future-Trends-by-PMR.html>] (accessed February 2016).
39. CMR International, Thomson Reuters Business. Global Pharmaceutical Sales, London, 2015 [http://cmr.thomsonreuters.com/pdf/Executive_Summary_Final.pdf].
40. Research and Markets (http://www.researchandmarkets.com/research/xjrcm6/global_mineral) has announced the addition of the "Global Mineral Supplements Market Size, Share, Development, Growth and Demand Forecast to 2020" (accessed March 2016).
41. P& S Market Research, Global Vitamin Supplements Market (Size of \$37 billion in 2014) to Witness 7% during 2014–2020. April 2015 [<https://www.psmarketresearch.com/market-analysis/vitamin-supplements-market>] (accessed March 2016).

42. Dennehy C, Tsourosunis CV, Miller AE. Evaluation of Herbal Dietary Supplements Marketed on the Internet for Recreational Use. *Annls Pharmacother* 39(10), 1634-1639, 2005.
43. Bert F, Giacometti M, Gualano MR, Siliquini R. Smartphones and health promotion: A Review of the Evidence. *J Med Systems* 38,9995, 2-11, 2014.
44. Kennedy J. Herb and supplement use in the US adult population. *Clin Therapeut* 27(11),1847-1858, 2005.
45. Wilson KM, Klein JD, Sesselberg TS, Yussman SM, et al. Use of complementary medicine and dietary supplements among U.S. adolescents. *J Adolesc Health* 38(4), 385-394, 2006.
46. American Cancer Society (30/3/2015) [<http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternativemedicine/dietarysupplements/dietary-supplements-risks-and-side-effects>] (accessed March 2016).
47. Kirk S, Woodhouse A, Conner M. Beliefs, attitudes and behaviour in relation to supplement use in the UK women's cohort study (UKWCS). *Proc Nutr Soc.* 57, 54A, 1998.
48. Conner M, Kirk SF, Cade JE, Barrett JH. Why do women use dietary supplements? The use of the theory of planned behaviour to explore beliefs about their use. *Soc Sci Med* 52(4), 621-633, 2001.
49. Dickinson A, Blatman J, El-Dash N, Franco JC. Consumer usage and reasons for using dietary supplements: report of a series of surveys. *J Am Coll Nutr* 33(2), 176-182, 2014.
50. Baile RL, Gahche JL, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. *JAMA Intern Med* 173(5):355-361, 2013.
51. FDA, Safety Portal for dietary supplements [<http://www.fda.gov/Food/DietarySupplements/ReportAdverseEvent/default.htm>] (accessed March 2016).
52. Geller AI, Shehab N, Weidle NJ, Loverrove MC, et al. Emergency department visits for adverse events related to dietary supplements. *New Engl J Med* 373:1531-1540, 2015.
53. Klontz KC, Debeck HJ, Leblanc PA, Mogen KM, et al. The role of adverse event reporting in the FDA response to a multistate outbreak of liver disease associated with a dietary supplement. *Public Health Reports* 130(5), 526-532, 2015.
54. Ames BN., McCann JC, Stampfer MJ, Willett WC. Evidence-based decision making on micronutrients and chronic disease: long-term randomized controlled trials are not enough. [Letter to the Editor]. *Am J Clin Nutr*, 86, 522-525, 2007.
55. McIntosh J. Recalled dietary supplements still contain banned substances. *Medical News Today*, 22 October, 2014. [<http://www.medicalnewstoday.com/articles/284158.php>] (access Febr 2016).
56. Cohen PA, Maller G, DeSouza R, Kababick JN. Presence of banned drugs in dietary supplements following FDA recalls. *JAMA* 312(16), 1691-1693, 2014.
57. Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: an updated systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 159, 824-834, 2013.
58. Grodstein F, O'Brien J, Kang JH, Dushkes R, Cook NR, Okereke O, et al. Long-term multivitamin supplementation and cognitive function in men. A randomized trial. *Ann Intern Med* 159, 806-814, 2013.
59. Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E. Screening for cognitive impairment in older adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med.* 159, 601-612, 2013.
60. Lamas GA, Boineau R, Goertz C, Mark DB, Rosenberg Y, Stylianou M, et al. TACT (Trial to Assess Chelation Therapy) Investigators. Oral high-dose multivitamins and minerals after myocardial infarction. A randomized trial. *Ann Intern Med* 159, 797-804, 2013.
61. Guallar E; Stranges S, Mulrow C, Appel LJ, Miller III, ER. Enough is enough: Stop wasting money on vitamin and mineral supplements. *Ann Intern Med* 159(12):850-851, 2013.
62. Huang HY, Caballero B, Chang S, Alberg AJ, Semba RD, Schneyer CR, et al. The efficacy and safety of multivitamin and mineral supplement use to prevent cancer and chronic disease in adults: a systematic review for a National Institutes of Health state-of-the-science conference. *Ann Intern Med* 145, 372-385, 2006.
63. Bjelakovic G, Nikolova D, Gluud C. Antioxidant supplements to prevent mortality. *JAMA* 310, 1178-1179, 2013.
64. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med* 142:37-46, 2005.
65. Miller ER 3rd, Juraschek S, Pastor-Barriuso R, Bazzano LA, Appel LJ, Guallar E. Meta-analysis of folic acid supplementation trials on risk of cardiovascular disease and risk interaction with baseline homocysteine levels. *Am J Cardiol* 106, 517-527, 2010.
66. Moyer VA, U.S. Preventive Services Task Force. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 158, 691-696, 2013.
67. Gahche J, Bailey R, Burt V, Hughes J, Yetley E, et al. Dietary supplement use among U.S. adults has increased since NHANES III (1988-1994). *NCHS Data Brief* 1-8, 2011.

68. Oregon State University. Linus Pauling Institute. The case is far from closed for vitamins and mineral supplements. [<http://lpi.oregonstate.edu/case-far-closed-vitamin-and-mineral-supplements>] (accessed March 2016).
69. Fulgoni VL, III, Keast DR, Bailey RL, Dwyer J. Foods, fortificants, and supplements: Where do American get their nutrients?. *J Nutr* 141, 1847-1854, 2011.
70. Sebaqstina RS, Cleveland LE, Goldman JD, Moshfegh AJ. Older adults who use vitamin/mineral supplements differ from nonusers in nutrient intake adequacy and dietary attitudes. *J Am Diet Assoc* 107, 132-1332, 2007.
71. Shakur YA, Tarasuk V, Corey P, O' Connol DL. A comparison of micronutrient inadequacy and risk of high micronutrient intake among vitamin and mineral supplement users and nonusers in Canada. *J Nutr* 142, 1322-1332, 2012.
72. Stipanuk MH, Caudill MA (Eds). *Biochemical, Physiological, and Molecular Aspects of Human Nutrition*, 3rd edition, Elsevier Saunders, St Louis, MI, 2013.
73. Gaziano JM, Sesso HD, Christen WG, Bubes V, Smith JP, et al. Multivitamins in the prevention of cancer in men. The Physicians' Health Study II Randomized Controlled Trial. *JAMA* 308, 1871-1880, 2012.
74. Christen EW, Glynn RJ, Manson JE, MacFadyen J, Bubes V, et al. A multivitamin supplement and cataract and age-related macular degeneration in a randomized trial of male physicians. *Ophthalmology* Nov 20, 2013.
75. Maraini G, Sperduto RD, Ferris F, Clemons TE, Rosmini F, Ferrigno L. A randomized, double-masked, placebo-controlled clinical trial of multivitamin supplementation for age-related lens opacities. Clinical trial of nutritional supplements and age-related cataract report no 3. *Ophthalmology* 115, 599-607, 2008.
76. Hercberg S, Galan P, Preziosi P, Bertais S, Mennen L, et al. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med* 164, 2335-2342, 2004.
77. Heaney RP. Nutrients, endpoints, and the problem of proof. *J Nutr* 138, 1591-1595, 2008.
78. Wallace TC (Ed). *Dietary Supplements in Health Promotion*. CRC Press, Boca Raton, FL, 2015. Chapter 3. Rautianen S, Garziano M, Sesso HD. Assessing the potential for long-term effects of multivitamin supplements, pp. 55-73, 2015.
79. Watson RR (Eds). *Nutrients, Dietary Supplements and Nutraceuticals. Cost Analysis Versus Clinical Benefits*, Nutrition and Health. Springer-Science, Heidelberg, Berlin, New York. 2011.
80. Bergins K, Kreft S (Eds). *Dietary Supplements. Safety, Efficacy and Quality*. Woodhead Publishing, reprint of Elsevier, Amsterdam, New York, 2014.
81. Joshi S. Vitamin supplementation in the elderly. *Clin Geriatr Med* 31(3), 355-266, 2015.
82. Rumbold A, Ota E, Nagata C, Shahrook S, Crowther CA. Vitamin C supplementation in pregnancy. *Cochrane Database Syst Review* 2015 Sept 29:9:CD004072. DOI: 10.1002/14651858.CD004072.pub3.
83. Sparling TM, Henschke N, Nesbitt RC, Gabrysch S. The role of diet and nutritional supplementation in perinatal depression: a systematic review. *Matern Child Nutr* 3.2.2016, Epub ahead of print, DOI: 10.1111/mcn.12235.
84. Dangour AD, Allen E, Clarke R, Elbourne D, Fletcher AE, Letley L, et al. Effects of vitamin B-12 supplementation on neurologic and cognitive function in older people: a randomized controlled trial. *Am J Clin Nutr* 102(3), 639-647, 2015.
85. Ruan J, Gong X, Kong J, Wang H, Zheng X, Chen T. Effect of B vitamin (folate, B6, and B12) supplementation on osteoporotic fracture and bone turnover markers: a meta-analysis. *Med Sci Monit* 21, 876-881, 2015.
86. Dharmaraian TS. Is vitamin supplementation appropriate in the healthy old? *Curr Opin Gastroenterol* 31(2), 143-152, 2015.
87. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of cancer in adults. *Cochrane Database Syst Rev*, 2014 Jun 23;6:CD007469. doi: 10.1002/14651858.CD007469.pub2.
88. Xiao L, Xing C, Yang Z, Xu S, Wang M, et al. Vitamin D supplementation for the prevention of childhood acute respiratory infections: a systematic review of randomised controlled trials. *Br J Nutr* 114(7), 1026-1034, 2015.
89. Mandair D, Rossi RE, Pericleous M, Whyand T, Caplin ME. Prostate cancer and the influence of dietary factors and supplements: a systematic review. *Nutr Metab (London)* 2014 June 16:11.30 DOI: 10.1186/1743-7075-11-30.
90. Rumbold A, Ota E, Hori H, Miyazaki C, Crowther CA. Vitamin E supplementation in pregnancy. *Cochrane Database Syst Review*. 2015 Sep 7; DOI: 10.1002/14651858.CD004069. pub3.
91. National Academy of Science. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*, Washington DC, National Academy of Science, 2010.
92. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin. Proc.* 81 (3), 353-73, 2006.
93. Reid IR, Bristow SM, Bolland MJ. Calcium supplements: benefits and risks. *J Intern Med* 278(4), 354-368, 2015.

94. Athgen O, Hiligsmann M, Bulet N, Reginster JY. Public health impact and cost-effectiveness of dairy products supplemented with vitamin D in prevention of osteoporotic fractures. *Arch Public Health* 14 Dec: 73:48 2015, DOI: 10.1186/s13690-015-0099-3.
95. Zheng YT, Cui QQ, Hong YM, Yao WG. A meta-analysis of high dose, intermittent vitamin D supplementation among older adults. *PLoS One* 10(1):e0115850, 2015.
96. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid GD. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *Br Med J* 2011, 342. DOI: <http://dx.doi.org/10.1136/bmj.d2040>.
97. Marik P.E., Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: A systematic review. *Clinical Cardiology* 32(7), 365-372, 2009.
98. Harrison RA, Summerbell CD, Ness AR, Moore HJ, Worthington HV, et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease, and cancer: systematic review. *BMJ* 2006. DOI: 10.1136/bmj.38755.366331.25, 24.3.2006.
99. Molino A, Gioia G, Rossi Fanelli F, Muscaritoli M. The role for dietary omega-3 fatty acids supplementation in older adults. *Nutrients* 6(10), 4058-4073, 2014.
100. Long AB, Ward WE. PUFAs, bone mineral density, and fragility fracture: findings from human studies. *Adv Nutr* 7(2), 299-312, 2016.
101. Kakoti BB, Hernandez-Ontiveros DG, Katakai MS, Shah K, Pathak Y, Panguluri SK. Resveratrol and omega-3 fatty acid: Its implications in cardiovascular diseases. *Front Cardiovasc Med* 2015 Dec 11:2:38. DOI : 10.3389/fcvm.2015.00038. eCollection 2015.
102. Gomez-Candela C, Roldan Puchalt MC, Palma Milla S, Lopez Plaza B, Bermejo L. The role of omega-3 fatty acids in diets. *J Am Coll Nutr* 34 Suppl 1, 42-47, 2015.
103. Maehre HK, Jensen IJ, Elvevoll EO, Eilertsen KE. ω -3 fatty acids and cardiovascular diseases: effects, mechanisms and dietary relevance. *Int Mol Sci* 16(9), 22636-22661, 2015.
104. Fleming JA, Kris-Etherton PM. The evidence for α -linolenic acid and cardiovascular disease benefits: Comparisons with eicosapentaenoic acid and docosahexaenoic acid. *Adv Nutr* 5(6), 863S-876S, 2014.
105. Frassinetti S, Bronzetti G, Caltavuturo L, Cini M, Croce CD. The role of zinc in life: a review. *J Environ Pathol Toxicol Oncol* 25(3), 597-610, 2006.
106. Maret W, Sandstead HH. Zinc requirements and the risks and benefits of zinc supplementation. Review. *J Trace Elem Med Biol* 20(1), 3-18, 2006.
107. Ota E, Mori R, Middleton P, Tobe-Gai R, Mahomed K, et al. Zinc supplementation for improving pregnancy and infant outcome. *Cochrane Database Syst Rev*. 2015 Feb, DOI: 10.1002/14651858.CD000230.pub5.
108. Mocchegiani E, Romeo J, Malavolta M, Costarelli L, Giacconi R, et al. Zinc: dietary intake and impact of supplementation on immune function in elderly. *Age* 35(3), 839-860, 2012.
109. Lomagno KA, Hu F, Riddell LJ, Booth AO, Szymlek-Gay EA et al. Increasing iron and zinc in premenopausal women and its effects on mood and cognition: a systematic review. *Nutrients* 6(11), 5117-5141, 2014.
110. Basnet S, Mathisen M, Strand TA. Oral zinc and common childhood infections--An update. *J Trace Elem Med Biol* 31,163-166, 2015.
111. Rayman MP. Selenium and human health. Review. *Lancet* 379, 1256-1268, 2012.
112. Vinceti M, Dennert G, Crespi CM, Zwahlen M, Brinkman M, et al. Selenium for preventing cancer. *Cochrane Datab Syst Rev*. 2014 Mar 30;3:CD005195. DOI: 10.1002/14651858.CD005195.pub3.
113. Wu TW, Tsai FP. Comparison of the therapeutic effects and side effects of oral iron supplements in iron deficiency anemia. *Drug Res (Stuttg)*, 2015 Dec 23 [Epub ahead of print].
114. Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev* 2015, July 22:7:CD004736. DOI: 10.1002/14651858.CD004736.pub5.
115. Baumgartner J, Barth-Jaeggi T. Iron interventions in children from low-income and middle-income populations: benefits and risks. *Curr Opin Clin Nutr Metab Care* 18(3), 289-294, 2015.
116. Lambert JD, Sang S, Yang CS. Possible controversy over dietary polyphenols: benefits vs risks. *Chem Res Toxicol* 20, 583-585, 2007.
117. Ernst E. The Risk-Benefit Profile of Commonly Used Herbal Therapies: *Ginkgo*, *St. John's Wort*, *Ginseng*, *Echinacea*, *Saw Palmetto*, and *Kava*. *Ann Intern Med* 136(1), 42-53, 2002.
118. Pittler M, Ernst E. Dietary supplements for body-weight reduction: a systematic review. *Am J Clin Nutr* 79(4), 529-536, 2004.
119. Bertoia ML, Rimm E, Mukamal KJ, Hu FB, Willett WC, Cassidy A. Dietary flavonoid intake and weight maintenance: three prospective cohorts of 124 086 US men and women followed for up to 24 years. *BMJ* 2016; 352. DOI: <http://dx.doi.org/10.1136/bmj.i17>.
120. Vamenta-Morris H, Dreisbach A, Shoemaker-Moyle M, Abdel-Rahman EM. Internet claims on dietary and herbal supplements in advanced nephropathy: truth or myth. *Am J Nephrol* 40(5), 393-398, 2014.
121. Hardy ML, Duvall K. Multivitamin/multimineral supplements for cancer prevention: implications for primary care practice. *Postgrad Med* 127(1), 107-116, 2015.

122. Harvie M. Nutritional supplements and cancer: potential benefits and proven harms. 2014:e478-86. DOI: 10.14694/EdBook_AM.2014.34.e478.
123. Novelle MG, Wahl D, Diequez C, Berneir M, de Cabo R. Resveratrol supplementation: Where are we now and where should we go? *Ageing Res Revs* 21, 1-15, 2015.
124. Lall RK, Syed DN, Adhami VM, Khan MI, Mukhtar H. Dietary polyphenols in prevention and treatment of prostate cancer. *Int J Mol Sci* 16(2), 3350-3376, 2015.
125. Martinez ME, Jacobs ET, Baron JA, Marshal JR, Byers T. Dietary supplements and cancer prevention: balancing potential benefits against proven harms. *J Natl Cancer Inst* 104(10), 732-739, 2012.
126. Gaziano JM, Sesso HD, Christen WG, Bubes V, et al. Multivitamins in the prevention of cancer in men. The Physicians' Health Study II Randomized Controlled Trial. *JAMA* 308(18),1-10, 2012.