



# Complex foods versus functional foods, nutraceuticals and dietary supplements: differential health impact (Part 1)

**KEYWORDS:** Complex foods, functional foods, nutraceuticals, food structure, synergy, human studies, health potential.

**Abstract** What differentiates natural complex foods from nutraceuticals and dietary supplements is food structure, this latter involving nutrient interaction and synergism, and a complex mixture at nutritional doses. Scientific evidence showed that functional foods, nutraceuticals and dietary supplements (FND) have failed stopping chronic diseases epidemics: most conclusions of recent meta-analyses and systematic reviews are lack of significant health effect and needs for further studies. Why such disappointing results? Probably because FND results from a curative and reductionist nutritional approach while complex foods participates in a preventive and holistic approach. Indeed, reductionism has led to fractionate foods, isolating compounds from them for use at supra-nutritional doses in FND. Holism considers foods as complex systems in which the whole is more than sum of the parts leading to more sustainable health effects, and technological treatments more respectful of food structure.

## INTRODUCTION: DEFINITIONS

Except water, all foods are a mix of several macro-, micro- and/or phyto-nutrients and are therefore complex systems. Thus, milk is a complex food and complex foods are not only solid foods. Generally, two categories of complex foods are distinguished: natural and processed. Among processed foods, those processed directly from the natural matrix (e.g., cooked meat), and re-combined foods from isolated ingredients issued from fractionation and refining processes (e.g., white bread) are distinguished. Processed food matrices may be classified as: 1) Colloidal dispersions like emulsions (butter, mayonnaise) and foams (chocolate mousse); 2) amorphous or crystalline phases (most food solids, e.g., starch); and 3) gel networks (e.g., some dairy foods).

Complex foods may be also classified in food groups like dairy products, cereals, legumes, etc. But, from a nutritional point of view, it seems that it is more useful to rank complex foods according to their degree of processing. This classification has been proposed by the research team of Monteiro et al. in Sao Polo and has led to the release of a new Brazilian food guide pyramid (1). Authors distinguish: 1) Natural and minimally-processed foods; 2) ingredients for culinary purposes, either at home or in food industry; 3) processed foods, and 4) ultra-processed foods, notably snacks, ready-to-eat meals and sweetened drinks. What is interesting with such a classification is that risk for main chronic diseases is associated with high and regular consumption of foods from group 4, not really with usual plant- and animal-based food groups (2-4).

Functional foods "are defined as products that resemble traditional foods but possessed demonstrated physiological

benefits", and nutraceuticals "are commodities derived from foods, but are used in the medicinal form of pills, capsules or liquids and again render demonstrated physiological benefits" (5). According to the Dietary Supplements Health and Education Act, a dietary supplement is a "product other than tobacco that is taken by mouth, that contains one or more vitamins, minerals, herbs or other botanicals, amino acids, substances supplementing the diet by increasing the daily dietary intake, or a concentrate, constituent, metabolite, extract, or combination of these, that is not represented as a food or as constituting a meal or the sole item of the diet, and that contains as part of its labeling the words dietary supplement" (6). Contrary to functional foods, nutraceuticals and dietary supplements are therefore made of refined ingredients, isolated nutrients, and/or herb extracts.

Because complex foods, functional foods, nutraceuticals and dietary supplements are very different in nature, the aim of this opinion paper is to discuss their respective health benefits within the perspective of holistic versus reductionist approaches as applied in human nutrition researches.

## THE NUTRITION TRANSITION AND THE REDUCTIONIST PARADIGM

It is important to consider why functional foods, nutraceuticals and dietary supplements have been developing more and more during these last decades. According to me, there are two main reasons for this:

1) The Nutrition Transition that has led to unbalanced diets: it is characterized by the transition from traditional foods, very few

processed/purified, to ultra-processed foods. In other words, nutritional density-high foods were progressively replaced by energy-dense and refined foods, leading to epidemics of obesity, type 2 diabetes, cardiovascular diseases, and cancers (i.e., diet related non-communicable diseases) (7). Today, we are therefore confronted by the triple burden of over- and under-nutrition, and nutritional deficiencies; and functional foods, nutraceuticals and dietary supplements are generally used to re-equilibrate and/or to cure such nutritional imbalances and deficiencies.

2) A reductionist paradigm applied to research in nutrition since decades: the reductionist approach splits reality into isolated entities to reach a more deep understanding of underlying mechanisms, from biology to fundamental physics (8-10). It is based on a linear cause-effect relationship and has led to consider foods as an only sum of nutrients. More globally, the danger of an extreme and dogmatic application of reductionism is to cut ourselves from reality, and in the end from societal issues that are, by definition, complex. While reductionism follows a bottom-up approach, holism follows a top-down approach (Figure 1) (8). Finally, reductionism has led general public to associate one food with only one or two nutrients, agro-food industry to fractionate and recombine foods - notably leading to marketing of functional foods, nutraceuticals and/or dietary supplements -, and researchers to associate one compound with one health effect, leading to reductive, contradictory and/or controversial nutritional recommendations (Figure 2) (9). As a result, the application of reductionism to nutritional researches has not impeded the development of worldwide epidemics of diet-related chronic diseases such as obesity, type 2 diabetes and cardiovascular diseases.

Also, in an editorial of 2012, Riso and Soldati explained that ingredients and/or supplements are encouraged "in condition of overweight and obesity, hypo-nutrition or underweight, marginal deficiency of several micronutrients, monotony of the diet, increased needs in specific physiological condition or for specific activities or environmental condition, aging" and that they are also promoted to improve well-being and/or to decrease disease risk (11). Authors then added that

"the market of food ingredients and supplements is growing very quickly in part due to the wide interest of the research directed to the identification and selection of new potential ingredients with functional and/or preventive characteristics and in part due to the increasing demand of groups of consumers particularly interested in the dietary approach to health and well-being" (11). In other words, functional foods, nutraceuticals and dietary supplements have been mostly developed to cure or to re-equilibrate an already unbalanced diet. They are more related to a pharmacological and curative approach while complex and natural foods are more related to preventive and holistic nutrition (e.g., considering dietary patterns rather than isolated foods, but also exercise and overall quality of life in epidemiological studies) before the disease occurs (8, 9).

### COMPLEX FOODS AND FUNCTIONAL FOODS, NUTRACEUTICALS AND DIETARY SUPPLEMENTS FROM A HEALTH PERSPECTIVE

If we now consider the French context - that reflects quite well that of other European countries, today, we have reached a paradox: while the theoretical mean life expectancy increases by three months each year, the Healthy Life Years decrease. For example, between 2008 and 2010, the Healthy Life Years in France decreased from around one year, which is very high (8). This leaves an increasing place for an unhealthy state which is very expensive, both humanly and economically. Obviously, functional foods, nutraceuticals, dietary supplements, and drugs have engulfed within this span of around 20 years of unhealthy life years (65-84 years old for French women). Pharmaceutical and agro-food industries have made huge benefits, but - to be honest - benefits were not really for the large public. Globally, a healthy nutrition or diets (in its broader meaning) might account for a gain of at least ten more years of healthy life, i.e., beyond 70 years old (12). The challenge is very relevant for preventive nutrition. And, epidemiological studies clearly show that a healthy and balanced diet involves more complex, natural and/or minimally-processed foods than refined and ultra-processed foods, the high consumption of these latter being generally accompanied with functional foods, nutraceuticals and/or dietary supplements.

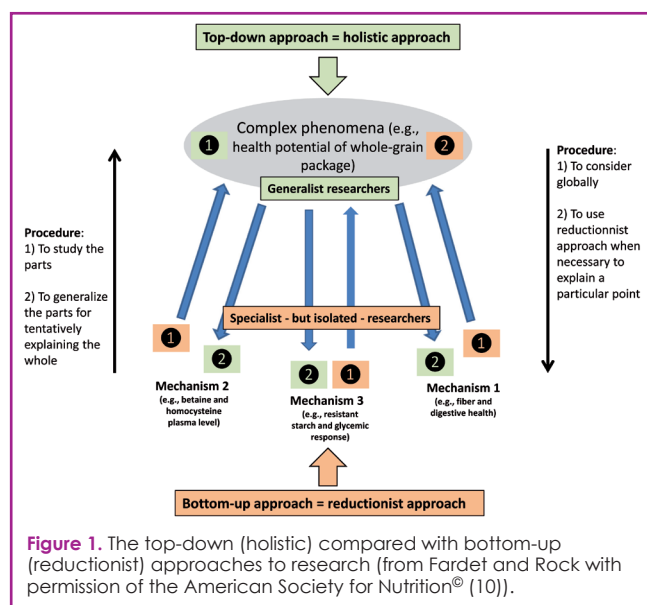


Figure 1. The top-down (holistic) compared with bottom-up (reductionist) approaches to research (from Fardet and Rock with permission of the American Society for Nutrition® (10)).

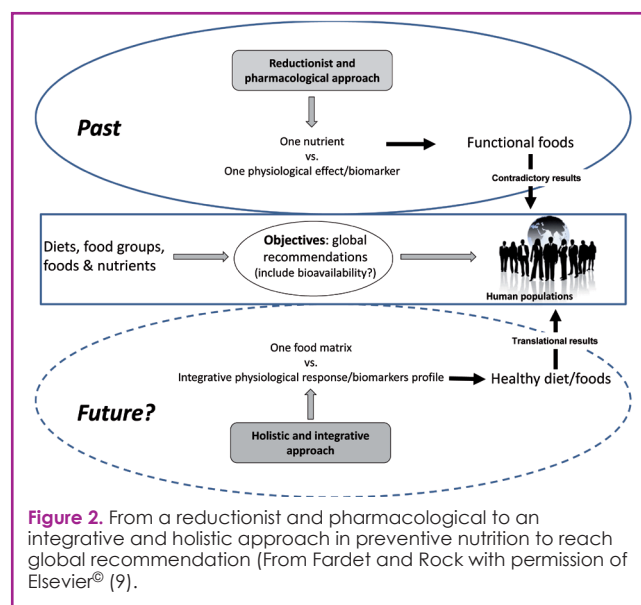


Figure 2. From a reductionist and pharmacological to an integrative and holistic approach in preventive nutrition to reach global recommendation (From Fardet and Rock with permission of Elsevier® (9)).

### **Complex foods versus functional foods, nutraceuticals and dietary supplements in human organism**

Several food parameters mainly differentiate complex foods from functional foods, nutraceuticals and dietary supplements, especially nutritional supplements:

- 1) While complex foods possess a structured matrix, nutraceuticals and dietary supplements are made of, somewhat, isolated compounds or ingredients, sometimes at supra-nutritional doses. Functional foods, although being complex foods, may also contain some compounds at supra-nutritional doses, e.g., phytosterols- or folates-enriched foods.
- 2) They exhibit different bioavailability and kinetics of nutrient release: while bioavailability is the percentage of a nutrient used by human organism for exerting a defined physiological action within body, kinetics of release is the way the nutrient is released and absorbed within digestive tract (e.g., slow versus rapid carbohydrates). Both bioavailability and kinetics of release importantly impact food health potential (13).
- 3) Complex foods supply to organism hundreds of bioactive compounds within a complex food environment, and these compounds may interact and act in synergy at nutritional doses; in addition, complex food structure may interact with digestive physiology such as satiety feeling, transit time or mucus secretion. On the contrary, dietary supplements supply a few (sometimes only one) bioactive compounds, generally at supra-nutritional doses.

In addition, if the dietary recommended intakes for main nutrients and some non-energy nutrients are known, the following important issue has never been really addressed: «Are differences in micronutrients/biofactors bioavailability and kinetics of release reflected in differential health effects?». The result of this gap, we do not hesitate to deliver to human organism high amounts of one isolated compound, free of food interactions and highly bioavailable, such as in some functional foods or antioxidant supplements. For example, phytosterol-enriched foods globally deliver 3-5 g of phytosterols a day to human organism, which is largely above nutritional doses (14).

### **Functional foods, nutraceuticals and dietary supplements and human studies**

What is about main conclusions regarding the preventive effects of functional foods, nutraceuticals and dietary supplements in humans? First, a strong trend can be extracted from scientific literature, notably from recent meta-analyses and systematic reviews: human interventional and observational studies investigating the health potential of supplements, functional foods, nutraceuticals and/or isolated bioactive compounds give unconvincing conclusions.

For example, recent conclusions of systematic reviews studying relation between dietary supplements and inflammation and hypertension are not convincing and further studies are needed, e.g., for plant-based ingredients versus inflammation in both healthy and unhealthy subjects (15, 16). Results were also very disappointing for antioxidants and cardiovascular risk: no convincing results have been obtained, notably with vitamins E and C and beta-carotene in both healthy and unhealthy subjects, and with folic acid in individuals at increased risk of cardiovascular disease (17-19). Thus, Riccioni et al. concluded that randomized controlled trials have failed to confirm the

benefits of vitamin C and E in cardiovascular prevention (17), Bjelakovic et al. concluded that there is no evidence to support antioxidant supplements for primary or secondary prevention,  $\beta$ -carotene and vitamin E seeming to increase mortality, and so may higher doses of vitamin A (the authors think that antioxidant supplements need to be considered as medicinal products and should undergo sufficient evaluation before marketing) (19), and Clarke et al. concluded that supplementation with folic acid to lower homocysteine levels had no significant effects within 5 years on cardiovascular events or on overall cancer or mortality (18). Moreover, in 2003, the conclusions of a WHO report about antioxidant supplements in both healthy and at risk subjects was: 1) the only convincing conclusion is the absence of effect of vitamin E supplement for cardiovascular diseases risk; 2) a possible increased risk of cardiovascular diseases with  $\beta$ -carotene supplements, 3) a possible decreased risk of cardiovascular diseases with flavonoids, and 4) insufficient scientific evidence for carotenoids vis-à-vis cardiovascular diseases, for zinc, selenium, flavonoids and carotenoids vis-à-vis cancers, and for vitamin E vis-à-vis diabetes (20). These results were confirmed in 2013 by Myung et al. in a meta-analysis of randomized controlled trials investigating effects of vitamins and antioxidant supplements in the prevention of cardiovascular diseases: a relative risk of 1.00 (95% confidence interval 0.98 to 1.02;  $I^2=42\%$ ) was found (21). However, there were significant protective effects of vitamins B6 and E supplementation in high quality trials but the authors noted that supplements were supplied by the pharmaceutical industry in these studies (21). Finally, Huang et al. concluded in 2006: "Evidence of human interventional studies is insufficient to prove the presence or absence of benefits from use of multivitamin and mineral supplements to prevent cancer and chronic disease (in healthy people)" (22).

Due to the growing interest for antioxidants by both large public and scientists, these conclusions clearly show that today a new paradigm to re-define antioxidants on the basis of new scientific results is needed. Indeed, 1) antioxidants have different modes of action (23); 2) they act in synergy to regenerate themselves (e.g., vitamin C regenerates vitamin E free radical tocopheryl and glutathione regenerate free radicals from vitamin C); 3) the dose effect is important and should not be put away as was shown with a mix of catechin and vitamin C (i.e., according to the dose ratio, the mix is either antioxidant or pro-oxidant) (24); and 4) kinetics of release differ according to the matrix (e.g., slow versus rapid ferulic acids have different modes of antioxidant actions) (25).

In addition to antioxidants, there is also the well-known example of phytosterols/phytostanols and of their potential hypocholesterolemic effect. Results of interventional studies in both normo- and hypercholesterolemic subject are also disappointing: they showed a modest cholesterol reduction by around 10-15% that has not succeeded in stopping cardiovascular disease risk; and a concomitant  $\beta$ -carotene absorption reduction of around 24%, such a decrease being compatible with the difference observed in subjects at risk of cardiovascular diseases (14). So, a paradox is reached: we first want to reduce cardiovascular disease risk but, in the same time, it could be increased via another physiological mechanism. Reasons for this is that, by isolating one compound from its initial and complex food environment based on a reductionist paradigm, some beneficial synergy effects are probably lost, and supra-nutritional doses are not really well controlled by human organism in the long term.



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Concerning fish oil supplementation on flow-mediated dilation (an index of endothelial function in humans), results also remain controversial as shown via a meta-analysis of randomized controlled trials in both healthy and unhealthy subjects (26). While results of pooled studies showed that fish oil supplementation significantly improved flow-mediated dilation, the quality of included studies was inversely related to the overall effect (26). Other mitigated effects have been revealed via meta-analyses, e.g., with vitamin D on lipid profile in both healthy and unhealthy subjects (27).

More conclusive results have been obtained with folic acid on total homocysteine levels in type 2 diabetic patients - although authors concluded that further longitudinal studies are warranted (28) - and on stroke prevention in ill subjects (cardiovascular, end-stage renal and esophageal dysplasia diseases) (29), with magnesium on reduced blood pressure in both normo- and hypertensive subjects (30) and on reduced plasma fasting glucose levels in type 2 diabetic subjects (31), and with calcium on bone density in postmenopausal women (32) and on pregnancy-induced hypertension and preeclampsia in pregnant women (33).

There are still many other meta-analyses and systematic reviews that show no convincing evidence of the effect of supplemental vitamins and minerals on various chronic diseases, but all cannot be cited here. Although functional foods, nutraceuticals and dietary supplements may be useful in some specific cases, on a long term, the more relevant solution is to encourage eating a diversified, nutrient-dense and complex food-based diet, together with increased physical activity. In other words, this means to shift from curative and reductionist to preventive and holistic nutrition.

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