Chapter 38

Functional foods

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'Functional food' has become a buzz word both in nutrition research and in the food industry. What are functional foods, and what is their relevance to nutrition and health?

38.1 What is a functional food?

There are many definitions of functional foods, but none official. A recent Consensus Document stated that a food can be regarded as 'functional':

> ... if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease.

The word 'functional' thus refers to the physiological functions which the food is intended to improve. A similar but simpler definition runs:

> Foods that may provide health benefits beyond basic nutrition.

Both these definitions focus on what functional foods do. This emphasis on the properties and actions of functional foods obscures one vital aspect, namely the marketing aspect. For example, sunflower oil reduces plasma cholesterol and the risk of coronary heart disease (CHD), but few people would refer to a generic bottle of sunflower oil as a functional food. However, if a manufacturer developed a proprietary brand of sunflower oil and marketed it with a cholesterol claim then that oil could well be called a functional food.

Thus, a functional food is usually a branded product that carries a health claim. The health claim is its hallmark. However, the health effect is usually not unique to the food in question. For instance, there is epidemiological evidence that a high intake of tomatoes is associated with a reduced risk of prostate cancer and other cancers, and this effect is ascribed to the lycopene in which tomatoes are rich. A manufacturer might therefore develop a tomato drink that is rich in lycopene and market it as a functional food, even though the effect of this functional food does not differ from that of other products made from tomatoes but marketed without a health claim. The health effect is thus usually based on pre-existing publicly available knowledge. Present-day functional foods rarely contain unique or new ingredients; the newness is mostly in the way in which

substances with known or supposed beneficial actions are incorporated into a palatable and attractive food that can be patented and marketed. Thus functional food research takes over where nutrition research ends, namely *after* a beneficial effect of a food or food ingredient has been discovered. Functional food research then develops a food that incorporates this ingredient. The research that is still required is a demonstration that the ingredient still has the claimed action after incorporation into the food in question.

The development of functional foods thus involves food technology and marketing over and above nutrition research. A better definition of a functional food might therefore be

> A functional food is the translation of nutritional knowledge into a commercial product with a health claim.

Thus, what distinguishes a functional food from an ordinary food is not its composition or its physiological effects but the way in which it is marketed. Most functional foods contain one or more active ingredients on which the health claim is based. It is therefore helpful to view a functional food as an active ingredient that is surrounded by three layers:

1. The food matrix (e.g. orange juice, chocolate, or margarine).
2. The package, which carries the ingredient list and the health claim. In most countries, these communications are regulated by law.
3. Unregulated communications, for example press releases, flyers, or sponsored articles in the media.

The active ingredient can also be packaged in a capsule or tablet. In that case, it is often called a dietary supplement because most people feel that functional foods are foods not pills while supplements are more similar to over-the-counter drugs. However, the border between foods and supplements is vague. Nutraceuticals or nutriceuticals can be either foods or supplements; there is no consensus about what these terms mean.

38.2 Why so much interest in functional foods

The emergence of functional foods, supplements and other forms of self-medication goes together with a number of social changes. People in developed countries are nowadays better educated, more knowledgeable about health, and more affluent than before, and they rely less on medical authorities. The passage of the Dietary Supplements and Health Education Act in the US illustrates this. Although its passage was preceded by intense industrial lobbying (http://www.prwatch.org/prw_issues/1997-Q3/index.html visited 31 October 2000), it also reflected a challenge from groups of citizens to what was seen as a paternalistic government that prevented people from deciding themselves what was good for them.

38.3 Health claims and the law

Functional foods tend to be more expensive than 'ordinary' foods, and the price is justified by the claimed beneficial effect on health. However, unlike taste or convenience, the health effect of a food cannot be perceived directly by the consumer; this is why it has to be communicated in the form of a health claim.

The trustworthiness of such health claims is largely dependent on government regulation. Such regulations differ widely between countries. Many countries do not allow 'medical' claims that refer explicitly to a disease, though some do; thus, stanol and sterol margarines are allowed to claim a beneficial effect on heart disease in the United States but not in Europe.

The United States has strict rules for foods but not for supplements. Health claims for foods are regulated in laws enforced by the US Food and Drug Administration (FDA). In contrast, FDA oversight over supplements was much reduced in 1994 when the US Congress passed the Dietary Supplements and Health Education Act. Under this act, manufacturers need to provide only limited evidence for the efficacy and safety of dietary supplements.

The European Union has rules for 'novel foods'. The rules were drawn up especially with a view to genetically modified foods, but they also apply to functional foods with new ingredients. However, these rules focus on safety rather than on the validity of nutritional claims.

European Union rules for medical and health claims for foods do exist but they are interpreted somewhat differently in different countries, although most do prohibit 'medical' claims. For instance, in the Netherlands health claims for supplements are not regulated in detail by the government; the industries involved have drawn up a list of claims that are permitted or not. The reasoning is often hard to follow: thus 'good for the blood pressure' is permitted, but 'for a good blood pressure' is not.

Paradoxically, the ban on medical claims also makes it illegal in some countries to state well-established effects of nutrients on disease in the form of a health claim. Thus, it is illegal in the Netherlands to claim that folic acid supplements prevent neural tube defects. (http://www.koagkag.nl visited 31 October 2000). This is particularly unfortunate because many women who plan to become pregnant fail to take folic acid supplements, and thus risk a serious disease in their offspring. Thus, the concern of the authorities to prevent misleading medical claims on foods may do harm when it prevents consumers from learning about foods or supplements that may actually prevent or cure a disease.

The interest of both industry and the public in branded foods with a health claim offers an opportunity to improve public health. Industrial sponsoring can bring an impetus to research; this research may result in healthy new products, and industry knows how to entice consumers into actually eating these products. Combining scientific and industrial know-how could therefore lead to healthy foods that actually sell. However,

present legislation in many countries does not require that the health benefits claimed by functional foods are supported by proper scientific evidence. Without such legislation there is no impetus for industry to invest in research and prove that the health claims are valid. As a result, there is now a plethora of foods which carry a suggestion of a health benefit that has not been proven scientifically.

Proper legislation is thus essential to the success of evidence-based functional foods. Ideally, if a claim is true manufacturers should be free to advertise it; and, if the claim is untrue it should be suppressed by law.

38.4 Evidence for efficacy and safety

38.4.1 Types of evidence

Food vs pharmaceuticals Regulation is needed so that the suggested health benefits of a functional food are supported by solid scientific evidence and that such foods have no adverse effects. Thus, we should require evidence both for the safety and for the efficacy of functional foods. Criteria for the safety and efficacy of new drugs are explicit and extensive. Should we require the same level of evidence for functional foods?

I believe we do not, because there is an important distinction between food and drug research. Pharmacological research aims to produce new molecules which affect physiological processes. In contrast, nutrition deals with molecules that have been part of the diet of populations for many centuries. Studying associations between diet and health in free-living populations is a powerful way to generate leads for health-promoting foods. Nutritional epidemiology is the high-throughput screening system of nutrition science,[1] and it has generated numerous leads, many of which have already led to healthier foods. However, an epidemiological association usually is not enough to prove causality unless the relative risk is very strong. Unfortunately, relative risks in nutritional epidemiology are typically weak, and then confounding by some other aspect of lifestyle is a serious problem. Thus, a combination of research approaches is needed to show that a functional food is effective and safe. Table 38.1 lists the types of research applied in nutrition, and their strengths and weaknesses.

Cell studies True understanding of how a nutrient affects health requires insights at the molecular level, and molecular biology has made enormous progress. However, extrapolation from (sub)cellular studies to the entire human organism is fraught with risk; the conditions *in vitro* may be far away from what happens *in vivo*. It has been stated appropriately as follows:

> ... our understanding of biologic mechanisms remains far too incomplete to predict confidently the ultimate consequences of eating a particular food or nutrient (W. Willett, *Nutritional Epidemiology*, Oxford University Press, 1998)

1 I gratefully acknowledge Peter Zock for this formulation.

Table 38.1 Types of research used to investigate the relation between diet and disease, and the strengths and weaknesses of the various approaches

Type	Strengths	Limitations
(Sub)cellular studies	Mechanistic insights	Extrapolation to entire human organism uncertain
Animal feeding trials	Long-term; hard end points: show cause-and-effect	Extrapolation to humans uncertain; conditions often extreme and unphysiological
Hereditary diseases	Human; long-term; hard end points; show cause-and-effect	Mutation may act through other paths than the one of interest (pleiotropic mutations); effects involved are often extreme
Randomized trials with surrogate end points	Human; controlled; show cause-and-effect	Short duration; validity of surrogate end points uncertain
Epidemiologic observations	Long-term; hard end points; applicable to general populations	Confounding; associations do not prove causality
Randomized clinical trials	Hard end points; show cause-and-effect	Duration sometimes too short; selected groups

Thus, cell and sub-cellular studies are an adjunct to nutrition research but cannot by themselves establish efficacy and safety.

Animal research Animal feeding trials have been a prime source of knowledge on nutrition and health, from the thiamin-deficient chickens which helped Eykman and Grijns to discover the first vitamin B_1 down to recent findings on the anti-arrhythmogenic effects of polyunsaturated fatty acids. Such trials offer hard end points and good dietary control, but extrapolation to man is uncertain. The question how to establish that an animal 'model' is indeed a proper model for human disease has not been solved. Thus, animal experiments can generate leads and offer corrobarative but not definitive evidence.

Hereditary diseases Hereditary diseases are an important source of information. Once the nature of the mutation in familial hypercholesterolemia had been cleared up the conclusion that high levels of LDL-cholesterol cause CHD became inescapable. The suggestion that high homocysteine levels cause cardiovascular disease was also inspired by observations in patients with homocysteinuria. However, even these 'experiments of nature' are not foolproof, because a mutation may act through another pathway than the one suspected; or through several pathways. Also, patients with inborn errors of metabolism often represent extremes, and extrapolation to milder conditions is not automatically justified.

Trials with surrogate end points Trials with surrogate end points measure the effect of diet on an intermediate disease marker such as cholesterol or blood pressure. Such trials are valuable because they show what happens in real people. However, the validity of surrogate end points is a point of concern. Even the best established markers can lead us astray. For instance, low-fat diets lower total serum cholesterol, and this was long equated with lowering of the risk of CHD. However, it is now clear that high-carbohydrate low-fat diets lower both the harmful LDL and the beneficial HDL cholesterol, and if both are taken into account the predicted effect on CHD risk is nil. Thus, even changes in established markers cannot be automatically equated with changes in the disease which they predict. Also, there are few validated markers outside the cardiovascular field; thus, one can measure the effect of diet on dozens of variables involved in immune response but the relevance of each of them to prevention of infection is still uncertain. Therefore, in spite of our understanding of human physiology, we still need experiments in which disease and death rates are explicitly observed.

Another concern about trials with surrogate end points is the potential for selective publication. Both authors and journals are usually less than enthusiastic about publishing a paper with negative findings, and an industrial sponsor may have a vested interest in having only those studies published that support his claim (Fig. 38.1). Hence, the totality of published studies may offer a biased view of what a food or ingredient really does. This may explain why meta-analyses of small studies may show beneficial effects of a food or ingredient while large experiments do not: large negative trials have a better chance of being published than small negative trials. This is partly because large trials are more interesting and convincing, and partly because the amount of time and money invested increases the pressure to publish.

Observational epidemiology Selective publication is also a problem in epidemiology, where one can test thousands of associations and then publish only the most appealing ones. Such 'data-dredging' has given epidemiology a bad name, but epidemiology remains the prime source of information on the long-term effects of foods on disease occurrence in humans. When epidemiological findings are consistent with other forms of evidence, causality becomes likely. Thus, neither the adverse effects of *trans* fatty acids on blood lipids in metabolic trials nor the association between *trans* fatty acids intake and CHD in epidemiological studies proved a causal link, but together they made a causal role of *trans* fat in heart disease highly likely.

Randomized clinical trials Randomized clinical trials with hard end points—i.e. disease and death—are considered the gold standard in biomedical research, and they indeed offer a level of confidence that no other type of research can match. The lack of randomized clinical trials in nutrition research puts nutrition at a disadvantage relative to pharmacological research. The costs of randomized clinical trials are often considered

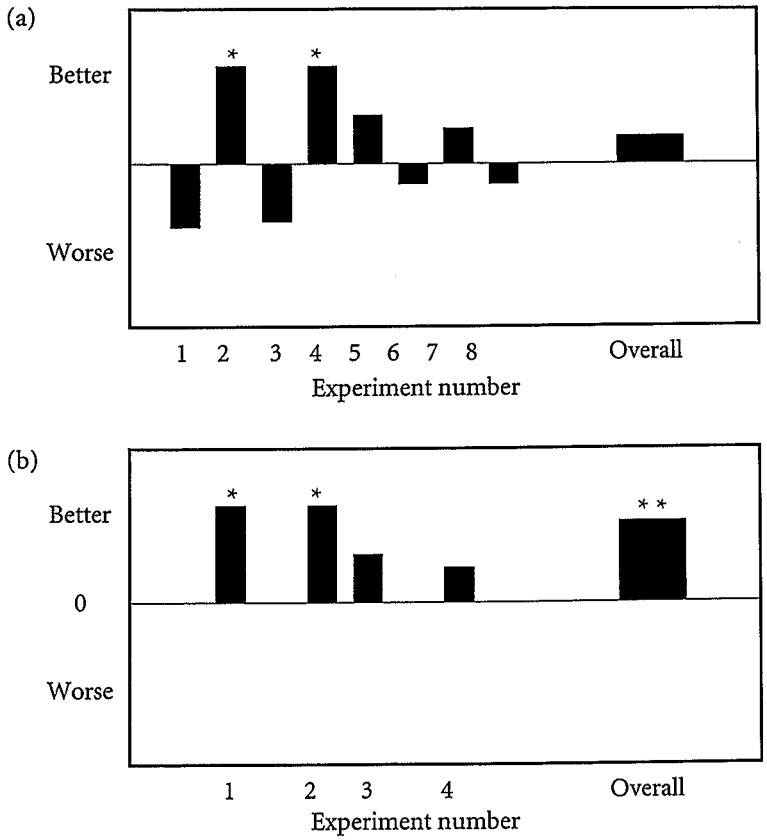

Fig. 38.1 Fictional representation of the effect of publication bias on the perceived health effect of a food ingredient. The vertical axis plots the effect of an imaginary food ingredient on some risk indicator for disease. Each bar represents the imaginary mean outcome of one published experiment. All experiments measured the effect of the same ingredient on the same risk factor; the differences between outcomes are due to chance and biological variability. (A) If all experiments are published then the mean overall effect in a meta-analysis is small and not significantly different from zero. (B) If experiments with nil or negative outcomes are not published then the mean overall effect in a meta-analysis becomes significant and favourable.

prohibitive, but the impact of a proper clinical trial is usually larger than that of a collection of smaller studies that together may have cost the same amount.

Randomized clinical trials also have their weaknesses. The chief of these is duration. Many benefits of diet may not be reaped within the 3–5 years of a randomized clinical trial, and a negative outcome is thus less than definitive especially if contradicted by the outcomes of observational epidemiological studies.

'Functional' effects of foods Proving that a food or ingredient actually improves health is thus a complicated, costly, and lengthy undertaking. The demands of the market put pressure on manufacturers to document health claims rapidly without incurring

the excessive costs needed to prove that a food really prevents disease. The middle road preferred by industry is to prove an effect on a 'function'. The 'function' can be a surrogate marker for disease but it could also be something as simple as showing that the active ingredient reaches the blood stream. Industry would like regulations in which various levels of evidence will permit various types of claims, some soft and some harder. Specifically, 'enhanced function' claims would concern beneficial effects on physiological functions or biological activities but would not require evidence of effects on disease. If such 'enhanced function' claims are permitted then advertising will probably convey them in a way that suggests an effect on health. To the consumer, the nuances of various classes of claims are moot; the only thing he is interested in is, 'Is this product good for me?' The message that every claim tries to convey is, 'Buy this product, it will make you healthier and make you feel better'. Consultants, seminars and conferences offer to teach food producers how they can communicate health effects of foods without breaking the law—and without having to prove definitively that the product actually improves health.

38.4.2 Conclusion

The costs of properly establishing that a functional food promotes health is huge, and understandably there is pressure from industry to adopt *in vitro* and 'functional' tests as a substitute for more expensive and lengthy studies. However, the history of β-carotene and cancer (Chapter 19) shows the risks of relying on soft evidence. If nutrition is to hold its own in an increasingly pharmacized world, we will need strict standards of evidence.

38.5 Promising areas for functional foods

There are functional foods and supplements on the market for just about any disease and organ including immune response, cancer, gastro-intestinal diseases, mood, memory and alertness, energy, strength and stamina, and ageing. However, the evidence for actual prevention of disease is often weak. Ageing is an attractive target in terms of marketing but it is not a disease or organ entity. The ills of old age fill textbooks; they are due to changes in arteries, bones, joints, muscles, eyes, ears, and the brain. The mechanisms involved in each may differ, and it is unlikely that a single nutrient or food will affect all of these changes.

The best-established diseases that can be prevented or cured through nutrition are of course the nutritional deficiencies, but cardiovascular diseases also offer a promising target. The following areas of research show potential.

38.5.1 Blood pressure

The effect of salt on blood pressure is well established although it is less marked than suggested by earlier research. There is also good evidence for a beneficial effect of

potassium. In addition, minerals such as magnesium and calcium offer promising leads. The dietary approaches to stop hypertension (DASH) trials have shown that fruits, vegetables and low-fat dairy products contain substances that lower blood pressure. Calcium and potassium are likely candidates for this, but folic acid and other plant constituents could also be responsible and await thorough testing.

Blood pressure is a well-validated biomarker for disease, and effects become visible within a few months. Research on the effect of components of vegetables and fruits on blood pressure is a promising but neglected avenue to new functional foods.

38.5.2 Blood lipids

High levels of LDL-cholesterol are a major cause of CHD, and foods that lower LDL have been marketed since the 1950s. Margarines high in linoleic acid were functional foods before the term was invented, and their efficacy and safety were established in randomized clinical trials of a size and quality that is nowadays rarely found in nutrition research. Margarines and other foods enriched in plant sterols and stanols effectively lower LDL and are the most credible of the new generation of functional foods. However, their safety and efficacy have not been established in clinical trials with hard end points.

38.5.3 Plasma homocysteine concentrations

Unlike lowering of blood pressure and LDL-cholesterol, lowering of homocysteine has not yet been shown to lower the risk of cardiovascular disease. Ongoing trials should answer this question in a few years time, and if lowering homocysteine helps, then the way is open to large numbers of foods and supplements that lower homocysteine. The effects of B-vitamins including folic acid on homocysteine are large, and new dietary effects on homocysteine await discovery.

38.5.4 Omega-3 polyunsaturated fatty acids

The United States Food and Drug Authority concluded in 2000 that the scientific evidence about whether omega-3 fatty acids may reduce the risk of CHD is suggestive, but not conclusive. Evidently, there is room here for further research. Evidence is the strongest for the very long chain omega-3 polyunsaturated fatty acids from fish, but the parent compound α-linolenic acid also shows promise.

38.5.5 Antioxidants

The antioxidant hypothesis has generated a large amount of research and great enthusisam among manufacturers of functional foods and supplements. However, proof has been slow in coming, and trials of the most promising antioxidant, vitamin E, have yielded disappointing results. In the absence of a valid biomarker for oxidation-related

disease, progress on the role of antioxidants in human disease has been slow but the final word has not been said.

38.6 Future of functional foods

Functional foods are already a booming market but for most of these products it is uncertain whether they will promote health. Nutrition research is laborious, and few universities nowadays maintain an active department of nutrition. On the plus side, development of intermediate markers for disease risk, such as imaging of carotid arteries with ultrasound, may make clinical trials of the effect of food on disease less costly, gene expression studies may provide new insights into mechanisms, and the functional food boom may bring extra funds for research. Still, nutrition research is expensive and slow, and the results will often fail to substantiate the high hopes of food producers. There is an urgent need for legislation that makes proper research both a requirement and a profitable underpinning for health claims. Otherwise, companies will forego rigorous testing and put foods on the market with unsupported health claims. The boom may then be short lived.

Further reading

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