



Food for thought

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Do certain kinds of food contain pharmacologically active substances in concentrations that are high enough to have druglike effects when consumed? Are biologically active compounds in food indicative of therapeutic value? Is traditional drug development suitable for testing the merits of food? Is it ethical to test food as a drug on patients? Will dietary disease management remain a pipedream? Is it a fact or fantasy that the Mediterranean diet is beneficial to health? Is a vegetarian diet an elimination therapy, or one of supplementation? What can be learned from animals? Are humans losing the capability of listening to their bodies? In this review, we will address these questions – providing food for thought.

Food, drugs and vitamins

Health food is, simply, food that is claimed to be healthy, either because it has a healthy image or because it contains ingredients that are commonly assumed to be healthy such as fiber, antioxidants and polyunsaturated fatty acids – good reasons to eat fruit, fresh vegetables, cereals and fish, or to drink green tea and red wine? In reality, there are only indications that such substances reduce the chances of contracting certain diseases. Health food can easily be distinguished from other foods that supposedly do not improve health or even cause health damage; for example, foods that are deemed unhealthy because they contain toxic ingredients, too few healthy ingredients or virtually no ingredients that are necessary for a healthy diet (e.g. ‘junk food’). ‘Functional’ foods are ‘...similar in appearance to a conventional food and are consumed as part of a usual diet, and impart some physiological benefit or a reduction in the risk of a particular chronic disease...’ [1], and all food for which this is not the case falls in the category of ‘non-functional’ food.

If you don’t eat, you die. If you eat too little, you get sick (e.g. malnutrition). If you eat too much you get sick (e.g. obesity). If you eat the wrong (i.e. poisonous) things, you get sick. All mushrooms, for instance, are eatable but many are not edible and can cause serious illness, cause hallucinations or even death. For example,

fly-agaric mushrooms (*Amanita muscaria*) contain the highly toxic muscarine which causes nausea and vomiting in the early stages of fly-agaric intoxication, and also ibotenic acid and its decarboxylation product muscimol which have strong hallucinogenic effects. The combined effects of these compounds cause the death of several people every year [2]. It is only when one eats the right things in the correct quantities that food intake does not influence health in a negative way. But can food have a positive effect on health? Can it be a therapeutic drug?

There are three categories of drugs: those that fight symptoms (i.e. virtually all drugs), those that take away the cause of a disease (e.g. antibiotics) and those that prevent diseases from happening (e.g. vaccines). In the Western world, the terms ‘drug’ and ‘single compound’ are often considered to be synonymous. This is an unjustified restriction. Extracts of St John’s wort (*Hypericum perforatum*) have been clinically proven to be effective in treating depression [3], and many traditional medicines, at least, share the efficacies of the active substances that they contain.

In many cases, apparently doing nothing will result in a patient becoming cured. This phenomenon is observed in all clinical trials: the placebo effect – the mysterious power hiding in every human being. According to how strong someone’s faith in an administered medicine is, the end result of treatment can vary substantially. The human mind can be an effective drug in almost all disorders.

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Vitamins are compounds that the human body cannot synthesize, and they must be supplied by the diet. The role of vitamins in human health is clear in the positive and negative sense. A popular and mistaken belief is that if a little of something is beneficial, more of it will be even better. This does not apply to vitamins. Overexposure to, notably, the fat-soluble vitamins has harmful effects on health. Chronic overdosing of vitamin D might result in a life-threatening hypercalcemia with bone, kidney and neurologic disease, overdosing vitamin E is known to have been the cause of hemorrhagic stroke, and overdosing vitamin A can cause loss of vision. The best case scenario with such overexposure is the production of waste – the reason why one of the richest natural sources of vitamin C is urine from Westerners [4]. Failure to intake vitamins inevitably results in serious diseases that can easily become fatal. For instance, lack of vitamin C results in scurvy, lack of vitamin B₁ causes beriberi and vitamin D deficiency will cause rickets. Vitamins can prevent and cure diseases – they are drugs by any definition. Vitamins simply must be present in sufficient quantities in a wide variety of food and in all inhabited areas. Otherwise humankind would not have survived to date. Many plants and animals used as food contain vitamins; all fitting the definitions of health food and functional food, and this underlines the fact that these terms have no scientific value. Vitamins leave us with some intriguing questions: are there vitamins for every disease, or at least for more diseases than we currently know of? Is it possible that there are vitamins that could prevent certain types of cancer if taken daily in a sufficient quantity? If this proves to be true, how can we identify them? Are there lessons to be learned from the story of how British sailors became known as ‘limeys’, or from the discoveries of other vitamins? [5].

Can food be a drug?

The question here is not whether food can contain compounds that might serve as leads for drugs, or that could become drugs themselves. This subject has already been discussed in the literature [6]. And it is not whether it is possible to add drugs to food. When one adds a compound such as aspirin to food, the food will have analgesic properties; when one adds a cholesterol-lowering drug to a certain foodstuff, this will no doubt have favorable cardiovascular effects, similar to those of the statins [7]. The resemblance between these types of functional foods and the ‘Emperor’s new clothes’ is apparent.

The true question is whether certain kinds of food contain pharmacologically active substances in sufficiently high concentrations to have a druglike effect when that food is consumed in reasonable amounts. The answer could be yes. Apart from the known vitamins, food might contain other compounds that can be drugs. The problem is how one can identify such foods. Identification, in most cases, is likely to be purely serendipitous. The chances that, in a rational process, one detects that eating a certain type of fruit or vegetable will prevent the occurrence of, for instance, Alzheimer’s disease are not very high, but the possibility cannot be excluded. In the past, it has been claimed that many plants and other foods have particular health benefits. The reaction of ever-vigilant entrepreneurs has been to extract compounds from the sources that are presumed to be responsible for claimed health effects and to market them, either as pure compounds or partly purified extracts. Hence, so-called nutraceuticals have

emerged (i.e. ‘...substances or combinations of substances consisting of molecules or elements, found in nature or food, for the purpose of maintaining or improving health and treating or preventing diseases...’, as can be read in nutraceutical industry advertisements). A problem for society is how to distinguish the good from the bad, or worse – the ugly. There are certainly ‘good’ nutraceuticals. A health claim approved by the AFSSA (Agence Française de Sécurité Sanitaire des Aliments), for Ocean Spray® products, is that cranberry juice can prevent urinary-tract infections. A dried and powdered garlic preparation (Kwai®) has been registered in Denmark as a cholesterol-lowering drug, and a fish oil extracted from cod, highly enriched in n-3 fatty acids (also known as omega-3 fatty acids), was registered in Norway as a drug for the prevention of secondary coronary infarction [8], it is marketed as Omacor®. There are indications that preparations such as this might also be of therapeutic value for treating arthritis [9] and central nervous system disorders such as developmental coordination disorder, which affects ~5% of children aged 5–12 years [10]. Apart from these few examples, where there is some evidence that nutraceuticals can have beneficial effects, the majority of claims can be considered as ‘bad’ because they are unsubstantiated (not in the least because, more often than not, their bioactive constituents are either unknown or speculative, making it impossible to standardize the product with regard to its expected effect [11]) or yet to be substantiated. Some nutraceuticals could eventually prove to be ‘ugly’ because concentration or unexpected chemical modifications, caused by their production and storage, might cause adverse effects or interactions with drugs that are not normally observed with the food products from which they were derived. The fact that such interactions are not purely hypothetical stems from well-documented observations that they can occur with normal food products as well. For example, grapefruit juice and broccoli were shown to have pertinent effects on cytochrome P450 metabolism, thereby influencing blood plasma levels of some drugs.

Examples of compounds (Figure 1), isolated from food, that have been claimed to be healthy include:

- (i) genistein (present in many foods, notably soy), which has been claimed to prevent cancer [12];
- (ii) allicin, which was demonstrated to have antidiabetic, antihypertensive and antithrombotic activities – and it seems obvious to ascribe the anecdotal positive health effects of onions and garlic to this compound;
- (iii) resveratrol, which occurs in many plant species, in particular grapes, has been claimed to be of value as an anti-inflammatory drug, based on its ability to inhibit cyclooxygenase (COX) [13];
- (iv) oleocanthal, which has recently been isolated from olive oil, has also been shown to be a COX inhibitor [14];
- (v) epigallocatechin-3-gallate, abundant in tea, is claimed to have antitumor activity [12];
- (vi) lycopene, which occurs in many different plants, notably in tomatoes, has been claimed to reduce the risk of cardiovascular diseases and prostate cancer [18].

Is this surprising? Perhaps not, a systematic study revealed that at least one-third of Swedish food plants have anti-inflammatory activity [15]. A possible explanation for these observations could be the presence of sulfoquinovosyl diacylglycerols (SQDGs),

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