ELSEVIER

Food for thought

Martin Tulp[1], Jan G. Bruhn[2] and Lars Bohlin[3]

[1] Solvay Pharmaceuticals, Research Laboratories Weesp, Department of Intellectual Property & Scientific Information, C.J. van Houtenlaan 36, 1381 CP Weesp, The Netherlands
[2] InBio, Institute for Bioactive Natural Products, Stråvägen 2, SE 175 44 Järfälla, Sweden
[3] Uppsala University, Division of Pharmacognosy, Department of Medicinal Chemistry, Biomedical Center, BMC Box 574, SE-751 23 Uppsala, Sweden

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.

Corresponding author: Tulp, M. (martin.tulp@solvay.com)

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2006.10.010

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 B_1 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 then 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) epigallocathecin-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),

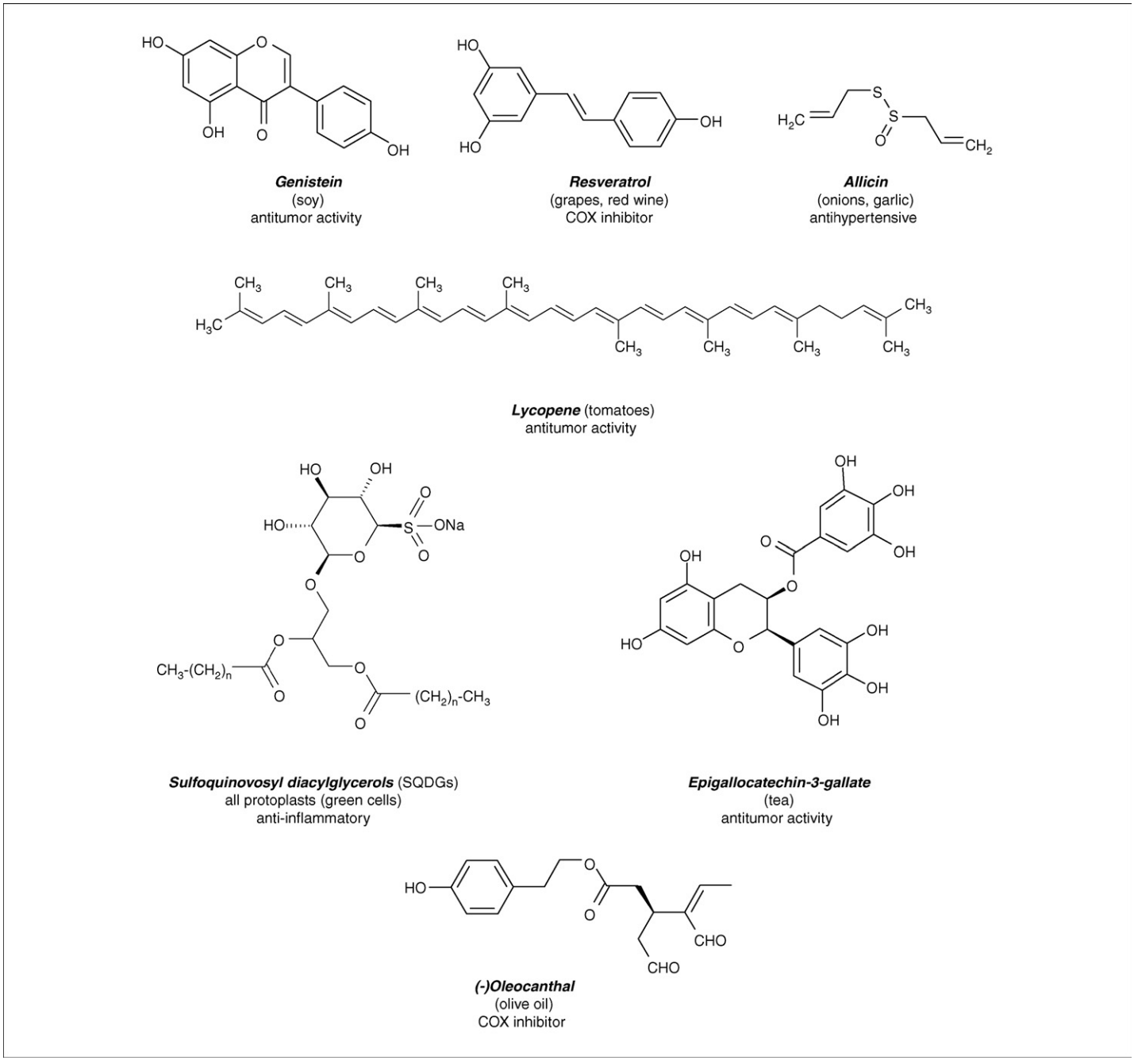

FIGURE 1

Biologically active compounds isolated from food that are claimed to be 'healthy'.

originally isolated from sea urchins, but later demonstrated to also be present in many vegetables, notably spinach. SQDGs possess anti-inflammatory activity and are among several chemicals intimately involved in photosynthesis [16]. Thus, they are present in every green cell (i.e. chloroplast) that we eat (i.e. in all green vegetables). Recently, SQDGs were identified as potent inhibitors of mammalian DNA polymerases and DNA topoisomerase II, and can be potent immunosuppressant and anticancer chemotherapy agents [17]

Research on food products, including spices, has resulted in the discovery of many compounds with interesting pharmacological properties, a few of which are listed, in pharmacopeias, as drugs useful in a variety of disorders. Examples are: theophylline (bronchodilatation: used in asthma and COPD); menthol (muscle relaxant: used in irritable bowel syndrome, bronchitis and sinusitis); sorbitol (diuretic: used in hypertension); and capsaicin (analgesic: used in diabetic neuropathic pain).

Food versus single compounds

It is a misconception that, for the pharmaceutical industry, it is a *condition sine qua non* to develop ultra-potent compounds with a single mechanism of action. As simple as it is ambitious, it is just to develop something effective. Major breakthroughs such as the first effective antidepressants, the tricyclics (e.g. amitryptiline), are compounds with many different activities at the molecular (i.e. receptor) level, and they are still very much in use. The same

applies to another breakthrough: the first effective antipsychotics (e.g. haloperidol) and, more so, to their subsequent generation – the 'atypical' antipsychotics such as clozapine and olanzapine. These compounds all have multiple mechanisms of action. Moreover, it is common practice that patients diagnosed with a particular disorder are prescribed more than one drug. When, sometime in the no doubt distant future, all of these drugs are replaced by foods, combined in a well-balanced diet, not even the shareholders of pharmaceutical industries will object.

When the term 'drug' is defined as something that will prevent or cure a disease, or alleviate its symptoms, then certain foods can be viewed as drugs, just like every single, purified or synthesized compound is now. When an animal model for a certain disease exists, in principle food and single compounds can be tested. Why is this never done? Is it the prejudice that food is not likely to contain individual components in concentrations that are high enough to be detected in a bioassay? Homogenates of poppies show up positive in analgesic bioassays so why should certain foods not be found to be active? There is no valid scientific objection against the testing of food in animal models with predictive value for specific diseases. If a foodstuff is active, it should follow the same protocols as every experimental single compound. It would be expected, however, that there would be at least one major difference: food, administered in practical quantities, would largely obviate the need for standard animal toxicity studies because it would be perceived to be material(s) that is generally recognized as safe (GRAS). Therefore, in quantities that are within normal boundaries when used as food, food can ethically be tested for pharmacologic properties in all diseases – effectively and without restriction. This represents a major advantage over experimental single compounds because to use them without strictly required toxicity data is illegal and unethical. So, is there a potentially bright future for food as a drug? Despite the benefits that have been mentioned, unfortunately it seems that this is not likely. The first problem to overcome is the question of how ethical it is to give a patient a certain food product in the hope that it will prove to be effective in a disease – especially when there is an existing, clinically validated treatment. This is likely to preclude testing food as a drug in every disease with a severe impact on quality of life. The only possibility where testing could occur is when a food product showed unequivocal effects in animal tests, with predictive value in combating such diseases. To acquire these data, testing in animal models is absolutely necessary. Screening is expensive and the pharmaceutical industry is unlikely to spend money on testing something that will never make a return on an investment. Suppose it had been demonstrated that eating two ounces of raw onions twice daily cured diabetes within a matter of weeks – this would be an observation and a discovery that could conceivably be patented, but the patent would be impossible to enforce because everybody can buy onions everywhere. It is impossible to enforce medical-use patents on food. Thus, it would be impossible to make money on such a discovery. For this reason, the pharmaceutical industry is highly unlikely to invest in clinical trials using foodstuffs as the potential therapeutic agent. The chances are that there will never be scientific evidence, in today's conventional sense, that food can be a drug.

Is any progress in our knowledge of the etiologies of diseases to be expected from food research? It is almost certain that this will be the case. Some substances found naturally in food cause forms of damage that are not usually thought of as food poisoning, partly because their effects are chronic rather than acute and partly because the pathogenic roles of many possible food toxicants are still uncertain. Examples of toxicants (Figure 2) [2,19] include:

(i) L-α-amino-β-oxalylaminopropionic acid, a compound from wild peas (*Lathyrus sativus*) and related species that, in times of food shortage, are part of the staple diets in Eritrea, parts of India and Algeria, and responsible for the neurotoxic syndrome called neurolathyrism;

(ii) L-hypoglycin, present in unripe akee plums (*Blighia sapida*), a compound that induces vomiting sickness in humans;

(iii) L-djenkolic acid, found, for example, in the djenkol bean (*Pithecolobium lobatum*), which is eaten in Java and causes acute kidney malfunction;

(iv) L-mimosine, present in several plants such as *Mimosa pudica*, which results in complete loss of hair in humans and animals such as horses, sheep and pigs;

(v) L-indospicine, found in leaves and seeds of *Indigofera* species (Leguminoseae), which is teratogenic, abortifacient and hepatotoxic in animals, and causes cleft palate and dwarfism in rats;

(vi) pristine, present in fish oil and anise fruits, among others, which causes arthritis in laboratory animals;

(vii) croton factor F_1 (12-*O*-palmitoyl-16-hydroxyphorbol-13-acetate), which occurs in the leaves of welensali (*Croton flavens*), which is commonly used in Curaçao to prepare welensali tea, thought to be the cause of the high incidence of oesophagal cancer in Curaçao;

(viii) tyramine, present in many foodstuffs – notably cheese and wine, which can induce an attack in migraine patients, and a comparable idiosyncratic reaction can occur in patients receiving monoamine oxidase inhibitors.

Is it conceivable that a single compound can be the cause of a disease? Not only is it conceivable but there are well-documented examples of this. In particular, 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP), an impurity isolated from meperidine (pethidine), a synthetic opiate, was found to cause the irreversible symptoms of Parkinson's disease in substance abusers [20]. In some patients, is it possible that Parkinson's disease might be caused by a hitherto unidentified food component, acting by the same mechanism as MPTP? Of the compounds illustrated here, no mechanism of action is known at the molecular level. As postulated by Ehrlich '*corpora non agunt nisi fixata*' [21]: for a compound to induce an effect it must act on a biological target. Thus, it must be possible to identify such receptors or enzymes. Perhaps these could serve as targets for new drugs. '*Sola dosis facit venenum*' [22] works both ways: not only does the dose determine whether or not a compound will be toxic it also determines whether or not a compound will have a therapeutic effect. When compared with prescription drugs, here lies a major drawback of food as a drug. Western medicine is based on the fact that many medicinal plants contain compounds that are useful as drugs. With very few exceptions, such compounds are used in their pure form, not as the original plants or extracts. One of the reasons for this is elegantly illustrated in the recent discovery of oleocanthal, a COX-inhibiting substance from olive oil [14]. The authors of this

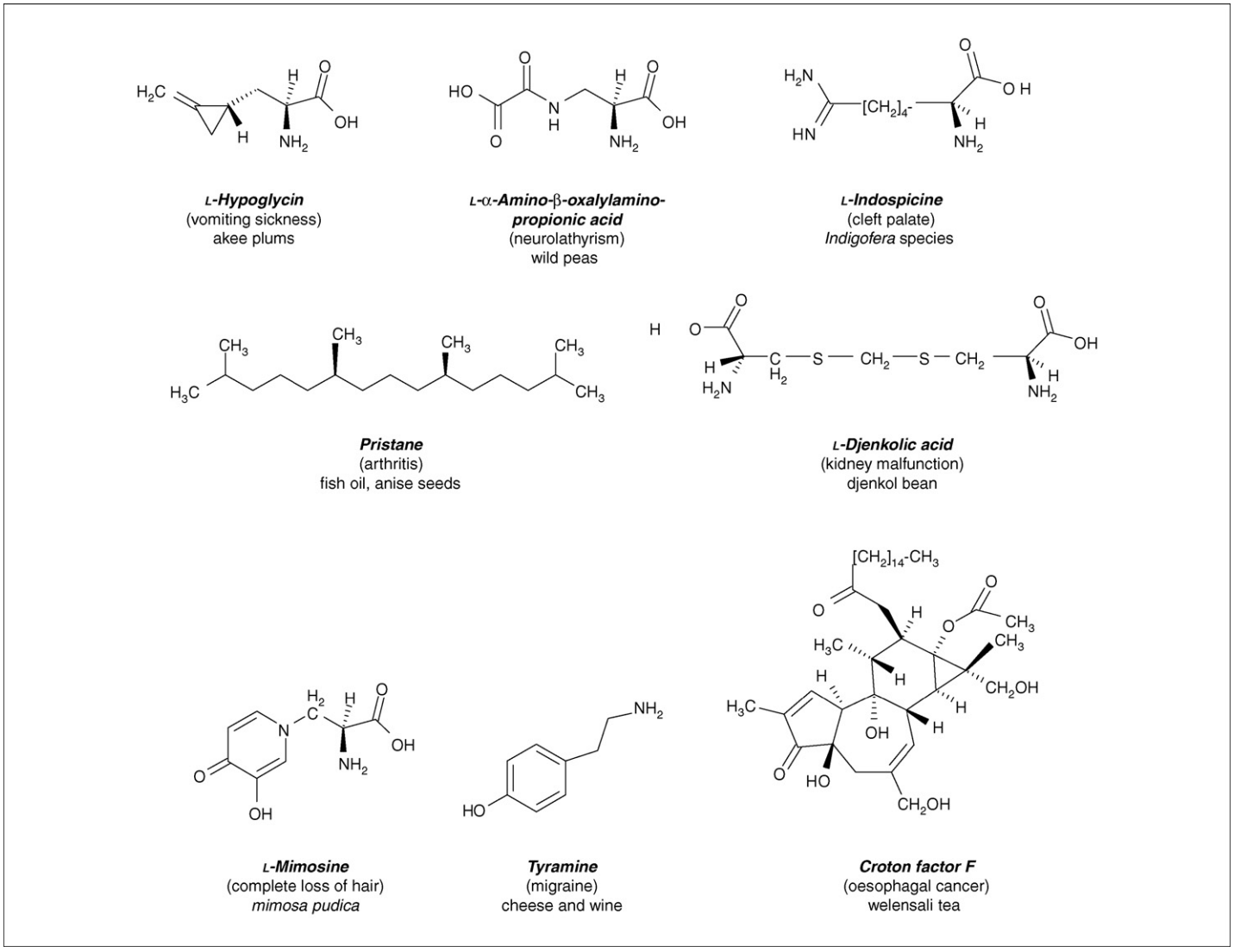

FIGURE 2

Compounds isolated from food sources that are directly linked to diseases.

article calculated that to ingest the amount of this compound equivalent to the recommended daily dosage of ibuprofen, one must swallow half a liter of extra-virgin olive oil. However, they also quoted that regular low doses of aspirin confer cardiovascular health benefits, could reduce the risk of developing some types of cancer, and perhaps also that of Alzheimer's disease. In other words, the discovery of the COX-inhibiting component of olive oil – so far only demonstrated *in vitro* – is cautiously brought forward as a mechanistic explanation of some of the various health benefits that the Mediterranean diet is claimed to provide.

Is dietary disease management a pipedream?

One glance at the sources of the compounds illustrated in Figure 1 and it can be seen that most of them feature prominently in Southern European cuisine. In recent years, many articles have been published on the Mediterranean diet, often claiming positive health effects. What is the possibility that these claims are true? What about the beautiful beaches, people, culture and, above all, the pleasant climate? Is it possible, or indeed probable, that these purported health effects have more to do with sunshine than anything else? Why do so many more Finnish people finish their lives by their own hands than people from Mediterranean countries? It is not likely that it is because of something that is wrong with their diet. History is full of sad hoaxes such as the Moerman diet, which claimed to cure cancer – unsurprisingly, it did not [23]. The ever-increasing human life expectancy must be attributed to improved healthcare, including progress in food conservation and preparation. Apparently, there are many variations on what might be considered a good diet. In addition, it is unlikely that diets have severe negative effects on health in general, although the increase in obesity in the West and the concomitant rise in conditions such as type II diabetes and other metabolic disorders seem to be evidence to the contrary. The question remains: can we improve on present diets?

There are indications that we can. For example, consider the enigmatic SQDGs. It is virtually impossible to avoid eating these compounds because they are ubiquitous in green plant cells. SQDGs are known to be anti-inflammatory agents, immunosuppressants and anticancer agents. Is it possible that people who are unfortunate enough to suffer from rheumatoid arthritis or cancer

must blame this on an insufficient diet? Or the reverse, does the disease-free population owe their health to a diet that is sufficiently rich in SQDGs? The number of clinical studies indicating that a vegetarian diet has a positive effect on the symptoms of rheumatoid arthritis is too large to ignore [24], and the same applies to the effects of diets low in arachidonic acid, with or without supplementation of fish oil [25]. However, the interpretation of these findings is a matter of dispute. Does a vegetarian diet represent an elimination therapy, resulting in a decreased intake of arachidonic acid; or is the substitution of meat by an increased intake of plant products – some with anti-inflammatory activity, as described – to be considered as supplementation therapy? Will it ever be possible to verify these hypotheses?

Regarding diet, what can be learned from animals? Observations that some, like humans, are omnivores and others are herbivores or carnivores suggest that there are many variations in mammalian diets, all of which are capable of maintaining reasonable levels of health. Animals eat what they want and the only proviso is that it must be available. Thus, although grizzly bears would eat salmon at all times of the year, they can only feed on them when the salmon enter rivers, on the way to their spawning grounds. Many animals choose to eat fruit, but they can only eat it when it is in season. When they do eat seasonable foods, they do so in a frenzy – rivaling pathological binge eating in humans. Through technology, humans have completely lost the need to eat food that is in season. Thanks to food conservation, greenhouses, deep-freezing and airplanes we can eat everything we want, in every season. Is this behavior that humans should maintain, or should humans behave like other animals? Could it be that eating large quantities of certain foods in season is nature's solution to the problem that low concentrations of druglike compounds are present in those foods? Animals have breeding seasons, presumably because offspring will be born when there is usually plenty of food. An alternative explanation could be that the right food is only available in certain seasons – a matter of quality rather than quantity. Harsh habitats can force some animals into hibernation, yet the environment also provides enough food to sustain these animals. Although animals are not aware of the concept of medicines, when they feel sick they sometimes eat plants they would not normally eat. For example, given the opportunity, cats and dogs eat certain species of grass to induce vomiting. Is zoopharmacognosy considered too primitive compared with pharmacognosy, or does it potentially add value because it is unbiased by human prejudices?

Why do people sometimes crave special foods? These cravings are phenomena collectively embraced under the term 'pica syndrome', named after the magpie (*Pica pica*): certain bizarre cravings for cornstarch, ice, clay and other substances have been linked to iron deficiency, but generally speaking food cravings are *terra incognita* as far as their molecular incentives are concerned. Why is it that, during pregnancy, women crave food that they would not normally long for? Is it because there is something in those substances that the body needs and, if so, how does the body know this? Is the answer in our genes? From what we know now about hormonal changes during the menopause, the pros and cons of hormonal replacement therapy and the existence of phytoestrogens in many plants, it should not be a total surprise to discover that postmenopausal women are naturally inclined to change their diet to include foods that are rich in estrogens. On an evolutionary timescale we are still animals. Therefore, it is not unthinkable that our bodies are still talking to us, and that we should, at least, consider listening to them.

From a health perspective it is easy to define what the ideal world should look like – one without disease. This could be achieved by finding drugs for every disease or, better than this, by identifying foods that can prevent disease. In the latter case the foods should be included in a regular diet. Ideally, for such foods, several alternatives should exist because, after all, who wants to eat the same thing every day? Is such an approach impossible? This fact is unknown but the pipedream should certainly be seriously considered for the future.

Concluding remarks and future perspectives

We know little, if anything, about the etiology of most diseases, and have great difficulty developing effective drugs. Thus, in the near future it seems to be unlikely that traditional research approaches will generate evidence in favor of food as drugs, let alone evidence that diet could prevent or cure disease.

Diets that are promoted by national or international nutritional societies usually target nutritional value: a balanced intake of proteins, carbohydrates, fatty acids, vitamins, minerals and trace elements. Their goal is to maintain health or to overcome the consequences of bad eating habits such as obesity and anorexia, which can be disastrous. However, when dieticians make health claims regarding druglike activity, science stops and 'religion' begins.

Fully varied diets provide the highest possibility that an individual will ingest components that positively impact health, but they also provide the highest possibility that harmful substances could be ingested. Based on the enormous diversity of food eaten by people, the fact that drugs are only active when administered in sufficient doses, and the fact that individuals vary greatly in susceptibility the results of epidemiological analyses on the health effects of foods must be treated with caution – there are simply too many variables.

Progress will be made with nutraceuticals. As discussed, some of these products have already proven to be clinically effective and have, therefore, obtained registration. It is possible that the results obtained can be translated back to the original food from which they were based. Also, in some instances, these translations could be practical in the sense that they can point towards beneficial effects of, for example, a 'reasonable' daily intake of garlic – rather than several pounds of it. The efforts made by the major food industries to put function into their functional foods, and the vast investments made in patentable nutraceutical research, are the most straightforward ways in which progress might be expected.

Perhaps the novel systems biology approaches [26], especially metabolomics [27], will create new inroads into the enigmatic subtleties of interactions between complex substances on healthy or diseased organisms with even greater complexity. Ethnopharmacological and, specifically, traditional Chinese medicines are multicomponent mixtures, just like foods are. When these approaches prove to be useful for understanding the effects of traditional medicines, the findings could translate to the health effects of specific foods. Unconventional studies, such as analyses of fecal water from humans on specific diets [28], probably provide diagnostic clues and might shed some light on the etiology of

certain diseases, generating novel incentives towards possible dietary therapies. Another potential route to follow would be studying individuals with genetic variations, compared with control individuals, to discover whether a specific gene is important in disease etiology. For instance, it was recently discovered that individuals with the Pro12Ala mutation modulate their bodyweight differently in response to the long-chain polyunsaturated fatty acids:saturated fat ratio [29]. Likewise, environmental stimuli are also beginning to be recognized as being capable of interacting with health.

Most of what has been said about food being healthy or unhealthy lacks conclusive evidence [30]. The effects of many health foods, functional foods and nutraceuticals have been blown out of proportion by clever advertising, unjustifiably supported by the media. Commercial hoaxes are commonplace, such as half-hype (i.e. halvarine), light-lunacy (i.e. Coca Cola Light), the caffeine-craze (i.e. decaffeinated coffee), the alcohol-obsession (i.e. alcohol-free beer) and organic-madness (e.g. organic meat, eggs, vegetables, and so on). Why do so many people spend money on these products of wishful thinking? The saying, 'a healthy mind in a healthy body' is no 'Holy Grail'. All that is required is some commonsense and a little discipline. For the time being, there seems to be one logical piece of advice: listen to your own body. When you have pleasure in eating something, it will be good for you. Beyond doubt, the same 'power' that enables a sick person to recover, even when he is given a placebo, will keep individuals healthy by eating the things they like. When it comes to food, whatever makes you feel good cannot possibly be bad for your health. Of course it is commonsense that eating must never result in abuse of one's body in terms of gross overweight. It is unlikely that being obese will make you happy. Sooner or later, it will make you miserable, physically and/or mentally. Or, as Hemingway wrote in *Time* (13 December 1954), 'I think body and mind are closely coordinated. Fattening of the body can lead to fattening of the mind'.

References

1 Hawker, G. (2002) Food: the ultimate delivery system? *Scrip Magazine* April, 14–17
2 Steglich, W. *et al.* eds (2000) *Römpp encyclopedia of natural products*, Georg Thieme Verlag, Stuttgart, Germany
3 Gastpar, M. *et al.* (2006) Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-IV and citalopram in patients with moderate depression: a double-blind, randomized, multicentre, placebo-controlled study. *Pharmacopsychiatry* 39, 66–75
4 Brigden, M.L. *et al.* (1992) High incidence of significant urinary ascorbic acid concentrations in a west coast population – implications for routine analysis. *Clin. Chem.* 38, 426–431
5 Watts, G. (2001) Twelve scurvy men. *New Scientist* 24 February, 46–47.
6 Tulp, M. and Bohlin, L. (2004) Unconventional natural sources for future drug discovery. *Drug Discov. Today* 9, 450–458
7 Simojoki, M. *et al.* (2005) Use of plant stanol ester margarine among persons with and without cardiovascular disease: early phases of the adoption of a functional food in Finland. *Nutr. J.* 4, 20
8 Harper, C.R. and Jacobson, T.A. (2005) Usefulness of omega-3 fatty acids and the prevention of coronary heart disease. *Am. J. Cardiol.* 96, 1521–1529
9 Curtis, C.L. *et al.* (2004) Biological basis for the benefit of nutraceutical supplementation in arthritis. *Drug Discov. Today* 9, 165–172
10 Richardson, A.J. and Montgomery, P. (2005) The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics* 115, 1360–1366
11 Van Boekel, M.A. and Jongen, W.M. (1997) Product quality and food processing: how to quantify the healthiness of a product. *Cancer Lett.* 114, 65–69
12 Park, O.J. and Surh, Y.J. (2004) Chemoprotective potential of epigallocatechin gallate and genistein: evidence from epidemiological and laboratory studies. *Toxicol. Lett.* 150, 43–56
13 Seaver, B. and Smith, J.R. (2004) Inhibition of COX isoforms by nutraceuticals. *J. Herb. Pharmacother.* 4, 11–18
14 Beauchamp, G.K. *et al.* (2005) Ibuprofen-like activity in extra-virgin olive oil. *Nature* 437, 45–46
15 Flodmark, C.A. *et al.* (2001) One-third of Swedish food plants has anti-inflammatory records. *Drug Discov. Today* 6, 455–456
16 Sato, N. (2004) Roles of the acidic lipids sulfoquinovosyl diacylglycerol and phosphatidyl-glycerol in photosynthesis: their specificity and evolution. *J. Plant Res.* 117, 495–505
17 Kuriyama, I. *et al.* (2005) Inhibitory effects of glycolipids fraction from spinach on mammalian DNA polymerase activity and human cancer cell proliferation. *J. Nutr. Biochem.* 16, 594–601
18 Canene-Adams, K. *et al.* (2005) The tomato as functional food. *J. Nutr.* 135, 1226–1230
19 Harborne, J.B. *et al.* eds (1999) *Phytochemical Dictionary: A Handbook of Bioactive Compounds from Plants*, Taylor and Francis Ltd, London, England
20 Langston, J.W. *et al.* (1983) Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. *Science* 219, 979–980
21 Ehrlich, P. (1913) Chemotherapeutics: scientific principles, methods and results. *Lancet* 2, 445–452
22 Von Hohenheim, T.B. (1589), *Liber paramixum*, Basel, Switzerland
23 Schraub, S. (2000) Unproven methods in cancer: a worldwide problem. *Support. Care Cancer* 8, 10–15
24 Ernst, E. and Chrubasik, S. (2000) Phyto-anti-inflammatories, a systematic review of randomized, placebo-controlled, double-blind trials. *Rheum. Dis. Clin. North Am.* 26, 13–27
25 Adam, O. *et al.* (2003) Anti-inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis. *Rheumatol. Int.* 23, 27–36
26 Verpoorte, R. *et al.* (2005) Ethnopharmacology and systems biology: a perfect holistic match. *J. Ethnopharmacol.* 100, 53–56
27 Wang, M. *et al.* (2005) Metabolomics in the context of systems biology: bridging traditional Chinese medicine and molecular pharmacology. *Phytother. Res.* 19, 173–182
28 Karlsson, P.C. *et al.* (2005) Human fecal water inhibits COX-2 in colonic HT-29 cells: role of phenolic compounds. *J. Nutr.* 135, 2342–2349
29 Scaglioni, S. *et al.* (2006) PPAR-{gamma}2 Pro12Ala variant, insulin resistance and plasma long-chain polyunsaturated fatty acids in childhood obesity. *Pediatr. Res.* 60, 485–489
30 De Roos, N.M. and Katan, M.B. (2003) Nutrition and health – sense and nonsense regarding food supplements and functional foods. *Ned. Tijdschr. Geneeskd.* 147, 56–60