Bioactive Components of Food

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Overview of bioactive compounds in foods

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Introduction

Food, besides supplying nutrients, contains a wide variety of bioactive substances, especially food of plant origin. The Swiss sage and physician Paracelsus (1493–1541) regarded plants as being a source of food, medicine and poison. He noted that ‘All things are poisons and nothing is without toxicity. Only the dose prevents anything not to be poisonous’. The term toxicity is generally regarded as the ability of a substance to cause injury when tested in isolation, whereas the term hazard is regarded as the ability of that substance to cause harm under the conditions in which it is used. Risk can be regarded as a measure of hazard. In recent years it has been recognized that bioactive compounds may confer benefits to health, rather than harm. An obvious example is that of ethanol where moderate intakes appear to decrease risk of cardiovascular disease and all-cause mortality in middle-aged and elderly men and women [1]. On the other hand, the same dose of alcohol in a young woman confers an increased risk of premature mortality from cancer [2]. Moreover, even moderate alcohol consumption will have adverse effects on those with liver disease. Thus the risk to an individual from bioactive materials in food and drink depends not only upon the potency of the substance, dose, duration and timing (exposure) but on the age, gender and health of the individual. The term phytochemical is often used to refer to xenobiotics from plants. It follows that the more varied the diet, the greater the chances of being exposed to phytochemicals. Most phytochemicals induce enzymes that lead to their breakdown and elimination. As this system is immature in early life, it is probably advantageous for young children to eat a diet that seems monotonous to an adult.

Toxic food constituents

Bioactive compounds that are found in staple foods or drinks are potentially those most likely to influence risk. However, enthusiasts for a particular food are a special group that deserve attention. Several edible fungi contain hydrazine derivatives such as agaritine [3] that are potentially carcinogenic; while the average intake may pose a small hazard to health, the risk will be much greater in extreme consumers. The adverse effects of phytochemicals is usually more severe in poorly nourished populations. This is well illustrated by the recent epidemic of nutritional optic nerve atrophy in Cuba [4], which has been related to cyanide intoxication in the presence of vitamin B₁₂ deficiency and a low methionine intake. Similar neuropathies occur in parts of the world where cassava is widely consumed. Cyanide intoxication in food is rare in developed countries, although the occasional fatal case has occurred in health food enthusiasts consuming apricot kernels, which contain amygdalin, a cyanogenic glycoside. Economic circumstances may force populations to consume certain plants in larger amounts than normal thus resulting in toxicity. This is well illustrated by the continuing problem of endemic lathyrism, a disorder that results in motor neuron damage and paralysis in Ethiopia and the Indian subcontinent. It is caused by the presence of the neurotoxin 3-N-oxalyl-2,3-diaminopropanoic acid in the seeds of Lathyrus sativa, which are consumed in excess in times of food shortage [5]. Risk of mycotoxicosis is also much greater in developing
countries, especially those with tropical climates and where conditions for food storage are poor [6]. Aflatoxin contamination of nuts, legumes and grains contributes to liver damage and probably liver cancer in Asia, and ochratoxin contamination of cereals has been linked with nephropathy in the Balkans [7]. In developed countries, exposure to mycotoxin is minimal. However, detectable levels of aflatoxins have been found in wholemeal peanut butter, nuts and dried fruit. Patulin has also been detected in apple juice.

It is perhaps a paradox that pulses, which are a food with a very healthy image, contain the widest diversity of bioactive substances many of which have well-documented adverse effects, such as lectins, cyanogenic glycosides, phytate, goitrogens, saponins and phytoestrogens. Fortunately most of the naturally occurring toxicants in beans are destroyed in cooking [8]. Red kidney beans cooked in a slow cooker have also caused poisoning because the temperature (60 °C) is not high enough to destroy the toxins. Pulses also contain unavailable carbohydrates (stachyose and raffinose) that are fermented to produce gases and are a major cause of flatulence. Documented cases of toxicity from phytochemicals in developed countries are uncommon. However, there have been a series of cases of a severe and sometimes fatal [9] fulminant hepatic failure resulting from the consumption of herbal teas containing pyrrolizidine alkaloids produced from Senecio vulgaris. Similar alkaloids are found in comfrey tea.

**Factors influencing mineral absorption**

Plant foods contain several bioactive compounds that interfere with the absorption of minerals particularly iron, calcium and zinc. Quantitatively the most important of these are phytates, but tannins, especially in tea, may also be important as inhibitors of iron absorption [13]. Phytates are a major cause of vitamin D and zinc deficiencies in parts of the world where diet consists of large amounts of unleavened cereals. In the last century rickets was strongly associated with the consumption of oatmeal, a rich source of phytates. It appears that diets high in phytates cause a mild hyperparathyroidism and increase the rate of calcification of 25-hydroxyvitamin D [14].

**Compounds with hormonal actions**

An interesting revelation is the discovery of compounds with hormone-like activity in plants. A 1,25-dihydroxyvitamin D glycoside was first discovered [15] in a South American forage plant (Solanum malacoxylon) and later in wild oats. When consumed as forage by cattle it resulted in signs of vitamin D toxicity. Licorice is known to contain glycorrhizic acid, which has mineralocorticoid properties. Indulgence in licorice can result in sodium retention and severe elevation of blood pressure [16]. Several compounds that show oestrogenic or anti-oestrogenic properties have been found in plants, especially legumes. Coumesterol and genistein are probably the most widely studied. Others such as zearalenone, a mycotoxin produced by Fusarium graminearum, are known to cause feminization in farm animals [8]. There is currently public concern about the levels of oestrogenic compounds arising from organic pollution. However, the levels of these compounds are much lower than those in plant foods [17]. For example, it is estimated that in terms of oestrogen equivalents (EQ), the average intake from bioflavonoids was 102 µg/day, compared with 2.5 pg/day for oestrogenic pesticides. In terms of anti-oestrogens measured as 2,3,7,8-tetrachlorodibenzop-dioxin anti-oestrogen equivalents (TEQ), the contribution from polycyclic aromatic hydrocarbons in food ranged from 1.2 to 5 ng/day, compared with an active derivative of indole-3-carbinol from Brussels Sprouts of 0.25–1.28 ng/day. It can be concluded that, with the exception of hormone administration, the major human intake of endocrine disruptors associated with the oestrogen-induced response pathways is from naturally occurring oestrogens found in foods.
The role of bioactive compounds in disease causation/prevention

The role of diet in the causation of chronic diseases such as cardiovascular disease, cancer and osteoporosis has become a major focus of public health nutritionists. These diseases are major causes of death and ill-health among the population. The major risk factors for cardiovascular disease (smoking, hypertension and hypercholesterolaemia) have been identified, but, besides smoking and excess alcohol intake, the risk factors for cancer are poorly understood. Obesity is a major contributor to ill health in the population and the incidence is rising dramatically as the population becomes less active and more indulgent. The intake of certain saturated fatty acids contribute, along with obesity, to elevated blood cholesterol concentrations. There is, however, evidence that bioactive materials in food may influence the risk of heart disease and cancer. Coffee consumption, for example, is strongly associated with increased risk of coronary heart disease and raised plasma cholesterol concentrations in some communities but not in others [18]. It appears that the method of preparation of the coffee is important, and two diterpenoid compounds have been implicated [19]. Fish consumption is associated with a decreased risk of heart disease independently of any effect on plasma cholesterol or blood pressure, and a trial of dietary advice to increase the intake of oily fish to twice a week resulted in a 29% reduction in all-cause mortality over the subsequent 2 years. This effect has been attributed to n–3 fatty acids present in fish [20]. It has been argued that certain polyunsaturated fatty acids may decrease susceptibility to cardiac arrhythmias.

The lower rates of heart disease in Southern Mediterranean countries despite their relatively high rates of smoking have led some to propose that there exists some protective element in the Mediterranean diet such as olive oil, red wine, garlic or fruit and vegetables. Such arguments have done much to promote the sales of olive oil and red wine as well as garlic preparations and anti-oxidant preparations containing carotenoids and flavonoids. However, to a large extent much of the variation can be explained by differences in saturated fatty acid and cholesterol intake between the populations [21].

Cancer

The role of diet in the causation of cancer is a controversial issue but as much as 35% of cancer risk may be explained by diet [22]. Animal studies suggest that a restricted energy intake is associated with a decreased risk of cancer. However, other dietary constituents may either be involved in offering protection against or causing cancer. Lower rates of cancer have been noted in vegetarians compared with meat-eaters even after adjusting for cigarette smoking and other lifestyle factors [23]. Several studies have shown a protective effect of fruit and vegetable consumption on colon and stomach cancer risk [24]. Green leafy vegetables and carrots are foods rich in carotene. A number of studies in humans have found lower plasma levels of β-carotene in individuals who subsequently developed cancer. It was consequently argued that β-carotene may decrease the risk of cancer by reducing free-radical attack, a process believed to be involved in the initiation of cancer. However, two large-scale randomized trials, the β-Carotene and Retinol Efficiency Trial (ACRET) and Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, in smokers found an increased risk of death from lung cancer with β-carotene supplements [25,26]. It may well be that free-radical-mediated reactions play an important role in decreasing cancer promotion.

Protection from cancer is most strongly associated with green leafy vegetables from the cabbage family rather than with carrots, even though they are the major source of carotene in the diet. It could be that green leafy vegetables also contain other substances that are protective [27]. One group of candidates are the characteristic pungent-tasting sulphur compounds (e.g. glucosinolates and S-methylcysteine sulphotioxide) in these foods. Although these compounds when fed in large amounts to animals induce thyroid cancers (because they mop up iodine), in smaller amounts they seem to have a protective effect against some types of chemically induced cancers in animals. The mechanism is believed to involve induction of drug-metabolizing enzymes in the intestine. Similar sulphur-containing compounds in garlic (allyl disulphide) have the same effect as cancer-blocking agents.

Nitrosamines are known to cause stomach cancer in animals and man. Nitrosamines are found naturally in many foods, such as edible
fungi, and can result from the reaction of nitrates with secondary amines, for example during the preservation of food with nitrites. Nasopharyngeal cancer in China is clearly linked to exposure in childhood to salt-pickled fish [28]. Stomach cancer rates have been declining in most developed countries but they are still high in many less economically developed communities. Changes in methods of food preservation from pickling and salting to refrigeration have probably played some part in the decline, as well as better food hygiene. For many years there has been a debate concerning nitrates and nitrites in food and risk of stomach cancer. It now seems that the cause of stomach cancer is repeated infection with *Helicobacter pylori*. There appears to be no positive relationship between nitrate in drinking water and food with stomach cancer. In fact, the consumption of vegetables that are the major dietary source of nitrate is associated with a lower risk of stomach cancer. Nitrates in vegetables may even protect against stomach cancer by killing *Helicobacter pylori* with peroxynitrite.

While stomach cancer has declined in developed countries, rates of colon cancer are rising, especially in Japan. An increased intake of dietary fat and a reduced intake of complex carbohydrate are associated with the increase in colon cancer [27]. Dietary constituents or modified intestinal secretions can supply carcinogens or co-carcinogens, the intraluminal concentrations of which may be modified by the presence of carbohydrate in the large bowel. Fermentation of carbohydrate, derived from non-starch polysaccharides and resistant starch, in the large bowel increases faecal bulk, leading to dilution of the large bowel contents and a faster faecal transit time, thus reducing the exposure of the large bowel mucosa to putative carcinogens. Short-chain fatty acids (SCFAs) produced during fermentation of carbohydrate decrease faecal pH and inhibit the degradation of bile acids and neutral sterols. Secondary bile acids are believed to promote carcinogenesis. Moreover, secondary bile acids are potent non-substrate inhibitors of glutathione S-transferase, which is involved in detoxification of exogenous carcinogens. Different substrates produce different patterns of SCFAs. It has been argued that certain SCFAs may stimulate apoptosis and therefore have an anticarcinogenic effect [29]. It may be possible to modify colonic bacterial flora by influencing substrate availability and by introducing specific bacterial cultures (probiotics) into the diet.

Conclusions

The use of specific food constituents to prevent or treat diseases is not a new concept. However, the term 'functional food' or 'nutraceutical' is being used to exploit consumer concerns about diet and health. Examples include the use of derived essential fatty acids such as γ-linolenic acid for premenstrual syndrome or n–3 fatty acids for inflammatory disorders such as rheumatoid arthritis. There is clearly a danger of increasing consumer expectations with such claims unless they are supported by well-controlled clinical trials. It may be important to consider compounds within their food matrix rather than in isolation. In practice, the toxicity of naturally occurring toxicants is usually spread over a number of receptors and some may be mutually antagonistic, so the net effect is zero. Food processing can lead to the destruction or removal of some bioactive compounds as well as generate novel compounds. In some cases this is desirable: for example the leavening of bread with yeast breaks down phytate and improves mineral availability; the heat treatment of soyabean flour reduces its toxicity by inactivating trypsin inhibitors. However, in other instances the effects are undesirable, for example the industrial catalytic hydrogenation of fats converts *cis*-unsaturated fatty acids into saturated *trans*-fatty acids, which overall have adverse effects on the risk of heart disease; the charbroiling of food leads to the generation of significant amounts of polycyclic aromatic hydrocarbons which are potential carcinogens and anti-oestrogens; the salting of food with nitrites leads to the formation of nitrosamines which are known carcinogens. Although the term 'natural' is widely used to convey a sense of wholesomeness and goodness, bioactive materials naturally present in food present a greater hazard to health than chemicals used in the production and processing of food.

3 Toth, B. (1991) In Vivo 5, 95–100
Introduction

Many inorganic nutrients, including iron, zinc and calcium, are incompletely and variably absorbed from the diet, and these differences in behaviour can be characterized in terms of bioavailability. The terms ‘bioavailability’ or ‘availability’ are sometimes used loosely to describe a number of ill-defined measurements relating to the absorption, retention or utilization of minerals, and even, misguidedly, to data generated from *in vitro* studies. The concept of bioavailability was originally derived from pharmacokinetic studies where measurements of the uptake of drugs into the circulation are made. However, with inorganic nutrients present in the diet, the generally accepted definition of bioavailability is the proportion of the total that is utilized for normal body functions. Mineral bioavailability is determined by dietary factors known to enhance or inhibit uptake into the body, as modified by host-related variables which regulate absorption and subsequent metabolism of the element. The complexity of these interactions necessitates careful planning of experimental protocols that are clearly focused on specific questions.

Methodological approaches

Iron was the first mineral to be selected for studies on bioavailability. Bioassays for iron were first published in 1926, shortly followed by chemical tests for ‘available iron’. A wide range of techniques have subsequently been developed to investigate iron bioavailability [1], as summarized in Table 1. Iron is the only inorganic nutrient for which it is possible to obtain a direct measure of bioavailability; this is accomplished using radio- or stable isotopes of iron to label the...