Functional Foods

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DEFINITION

The concept of functional foods derives from the observation that certain foods and beverages exert beneficial effects on human health that are not explained by their nutritional content (*i.e.*, macronutrients, vitamins and minerals). The definition of functional foods varies among countries for reasons that are historical, cultural and regulatory. In its broadest use, functional foods are food-derived products that, in addition to their nutritional value, enhance normal physiological or cognitive functions or prevent the abnormal function that underlies disease. A hierarchy of restrictions narrows the definition. In most countries, a functional food must take the form of a food or beverage, not a medication, and should be consumed the way a conventional food or beverage is consumed. If the ingredients are incorporated into pills, sachets or other dosage forms, they are considered dietary supplements or nutraceuticals, not functional foods. In Japan and Australia, the functional food appellation has been applied only to food that is modified for the purpose of enhancing its health benefits; in China, Europe and North America, any natural or preserved food that enhances physiological function or prevents disease might be considered a functional food. If food is modified, there is lack of international consensus as to whether a vitamin or mineral-enriched food (*e.g.*, folate-fortified flour or calcium-fortified orange juice) should be considered a functional food, or whether functional foods are described by the presence of their non-nutritive components (*e.g.*, fiber or polyphenols). Future development of functional foods is likely to be driven by scientific research rather than government regulation, so it is likely that the concept (if not the definition) of functional foods will remain fluid and flexible.

HISTORY

If the broadest, least restrictive definition is employed, the use of functional foods for promoting health and relieving symptoms is as old as the practice of medicine. Specific dietary recommendations for treating or preventing various types of illness have been documented in Hippocratic and Vedic texts and the canons of traditional Chinese medicine. Traditional Chinese remedies frequently contain recipes for combining specific foods with culinary and non-culinary herbs to produce healing mixtures. Folk medicine, East and West, has always depended upon functional foods. Peppermint (*Mentha piperita)* tea has a long history of use for digestive complaints. Peppermint oil contains spasmolytic components that block calcium channels in smooth muscle. Cranberry (*Vaccinium macrocarpon*) juice contains proanthocyanidins that inhibit the attachment of *E .coli* to the epithelium of the urinary bladder, explaining its efficacy in prevention of bacterial cystitis and its traditional use for treatment of urinary infection.

Herbs and spices are added to food to enhance flavor and initially were used to inhibit spoilage. Many of these have documented medicinal uses that render them functional foods, broadly defined. Thyme (*Lamiaceae spp)* was used as a vermifuge in ancient Egypt. Thyme oils possess potent antimicrobial properties. Ginger (*Zingiber officinale* root), cinnamon (*Cinnamomum spp* bark) and licorice (*Glycyrrhiza glabra* root) are common ingredients in Chinese herbal tonics and have been widely used in Western folk medicine for treating digestive disorders. Ginger contains over four hundred biologically active constituents. Some have antimicrobial, anti-inflammatory, or anti-platelet effects; others enhance intestinal motility, protect the intestinal mucosa against ulceration and dilate or constrict blood vessels. Cinnamon oil contains cinnamaldehyde and various phenols and terpenes with antifungal, anti-diarrheal, vasoactive and analgesic effects. Recent research has identified phenolic polymers in cinnamon with insulin-sensitizing and insulin-mimetic activity, leading to the recognition that regular consumption of cinnamon may help to prevent type 2 diabetes. The most studied component of licorice, glycyrrhizin, inhibits the enzyme11 beta-hydroxysteroid dehydrogenase type 2, potentiating the biological activity of endogenous cortisol. Glycyrrhizin also inhibits the growth of *Helicobacter pylori*. Glycyrrhizin and its derivatives may account for the anti-inflammatory and anti-ulcerogenic effects of licorice.

Fermentation is a form of food modification initially developed for preservation. The health-enhancing effects of fermented foods have a place in folk medicine. Several fermented foods have health benefits that exceed those of their parent foods and can be considered functional foods, broadly defined. These include red wine, yogurt and tempeh. Red wine is a whole fruit alcohol extract that concentrates polyphenols found primarily in the seed and skin of the grape. Its consumption is associated with protection against heart disease, perhaps because red wine polyphenols inhibit the production of free radicals and lipid peroxides that result from the simultaneous ingestion of cooked meat. Fresh yogurt contains live cultures of lactic acid-producing bacteria that can prevent the development of traveler's diarrhea, antibiotic-induced diarrhea, rotavirus infection, and vaginal yeast infection, decrease the incidence of post-operative wound infection following abdominal surgery and restore the integrity of the intestinal mucosa of patients who have received radiation therapy. Tempeh is made from dehulled, cooked soybeans fermented by the fungus, *Rhizopus oligosporus*. Not only is its protein content higher than the parent soybean, it has antibiotic activity *in vitro* and the ability to shorten childhood diarrhea *in vivo.*

Modification of a food to make it less harmful by removing potential toxins or allergens may create a functional food. Using this criterion, infant formula, protein hydrolysates, low sodium salt substitutes, low fat dairy products and low erucic acid rapeseed oil (canola oil) might be considered functional foods.

If the most restrictive definition of functional foods is employed, the functional food movement began in Japan during the 1980's, when the Japanese government launched three major research initiatives designed to identify health-enhancing foods to control the rising cost of medical care. In 1991, a regulatory framework, Foods for Special Health Uses (FOSHU), was implemented, identifying those ingredients expected to have specific health benefits when added to common foods, or identifying foods from which allergens had been removed. FOSHU products were to be in the form of ordinary food (not pills or sachets) and consumed regularly as part of the diet. Initially, eleven categories of ingredients were identified for which sufficient scientific evidence indicated beneficial health effects. The Japanese Ministry of Health recognized foods containing these ingredients as functional foods. They were intended to improve intestinal function, reduce blood lipids and blood pressure, enhance calcium or iron absorption or serve as non-cariogenic sweeteners (see Table One). In addition, low phosphorus milk was approved for people with renal insufficiency and protein-modified rice for people with rice globulin allergy.

Interest in the development of functional foods quickly spread to North America and Europe, where the concept was expanded to include any food or food component providing health benefits in addition to its nutritive value. In Europe, functional food proponents distinguished functional foods from dietetic foods, which are defined by law. European dietetic foods are intended to satisfy special nutritional requirements of specific groups rather than to enhance physiologic function or prevent disease through non-nutritive influences. They include infant formula, processed baby foods (weanling foods), low-calorie foods for weight reduction, high-calorie foods for weight gain, ergogenic foods for athletes, and foods for special medical purposes like the treatment of diabetes or hypertension. In the United States, functional food proponents have distinguished functional foods from medical foods, defined by law as special foods designed to be used under medical supervision to meet nutritional requirements in specific medical conditions. In both domains, functional foods have been viewed as whole foods or food components with the potential for preventing cancer, osteoporosis or cardiovascular disease; improving immunity, detoxification, physical performance, weight loss, cognitive function, and the ability to cope with stress; inhibiting inflammation, free-radical pathology and the ravages of aging; and modulating the effects of hormones. Researchers have sought to validate biomarkers that demonstrate functional improvement in response to dietary intervention, identify the chemical components of functional foods responsible for those effects and elucidate the mechanism of action of those components. The scientific substantiation of claims is a major objective.

In China, functional foods (referred to as health foods) have been viewed as part of an unbroken medical tradition that does not separate medicinal herbs from foods. Over 3000 varieties of health foods are available to Chinese consumers, most derived from compound herbal formulas for which the active ingredients and their mechanism of action are unknown, all claiming multiple effects on various body systems, with little experimental evidence for safety and efficacy but widespread acceptance due to their history of use.

EDIBLE PLANTS AND PHYTOCHEMICALS

Because their consumption is known to enhance health, vegetables, fruits, cereal grains, nuts and seeds are the most widely researched functional foods. The health benefits of a plant-based diet are usually attributed to the content of fiber and of a variety of plant-derived substances (phytonutrients and phytochemicals) with antioxidant, enzyme inducing and enzyme inhibiting effects. Some phytochemicals may also exert their health effects by modifying gene expression. Carotenoids, for example, enhance expression of the gene responsible for production of Connexin 43, a protein that regulates intercellular communication. The protective effect of carotenoid consumption against the development of cancer is more strongly related to the ability of individual carotenoids to upregulate Connexin 43 expression than their antioxidant effects or conversion to retinol. Dietary supplementation with beta-carotene reduces the blood levels of other carotenoids, some of which are more potent inducers of Connexin 43 than is beta-carotene. The unexpected and highly publicized increase in incidence of lung cancer among smokers taking beta-carotene supplements may be explained by this mechanism.

Phytochemicals associated with health promotion and disease prevention are described in Table 2. The most studied food sources of these phytonutrients are soy beans (*Glycine max*) and tea (*Camellia sinensis* leaves), but tomatoes (*Lycopersicon esculentum*), broccoli (*Brassica oleracea*), garlic (*Allium sativum*), turmeric (*Curcuma longa*), tart cherries (*Prunus cerasus)* and various types of berries are also receiving considerable attention as functional food candidates. An overview of the soy and tea research illustrates some of the clinical issues encountered in the development of functional foods from edible plants.

Soy protein extracts have been found to lower cholesterol in humans, an effect that appears to be related to amino acid composition. Soy protein extracts frequently contain non-protein isoflavones, which have received considerable attention because of their structural similarity to estrogen. Soy isoflavones are weak estrogen agonists and partial estrogen antagonists. Epidemiologic and experimental data indicate that isoflavone exposure during adolescence may diminish the incidence of adult breast cancer. *In vitro* studies show conflicting effects. On the one hand, soy isoflavones induce apoptosis of many types of cancer cells; on the other hand, estrogen receptor-bearing human breast cancer cells proliferate in tissue culture when exposed to isoflavones. Although the widespread use of soy in Asia is cited in support of the safety of soy foods, the intake of isoflavones among Asian women consuming soy regularly is in the range of 15 to 25 mg per day, significantly less than the isoflavone content of a serving of soy milk as consumed in the United States. In clinical trials, soy isoflavones have not been effective in relieving hot flashes of menopausal women but do diminish the increased bone resorption that causes post-menopausal bone loss. In pre-menopausal women, soy isoflavones may cause menstrual irregularities. The successful development of soy derivatives as functional foods will require that these complex and diverse effects of different soy components in different clinical settings be better understood.

Regular consumption of tea, green or black, is associated with a decreased risk of heart disease and several kinds of cancer. These benefits are attributed to tea's high content of catechin polymers, especially epigallocatechin gallate (ECGC), which has potent antioxidant and antiinflammatory effects, may lower cholesterol in hyperlipidemic individuals and alter the activity of several enzymes involved in carcinogenesis. Catechin content is highest in young leaves. Aging and the fermentation used to produce black tea oxidize tea catechins, which polymerize further to form the tannins, theaflavin and thearubigen. Although ECGC is a more potent antioxidant than theaflavin, theaflavin is far more potent an antioxidant than most of the commonly used antioxidants, like glutathione, vitamin E, vitamin C and butylated hydroxytoluene (BHT). Both ECGC and theaflavin are partially absorbed after oral consumption, but a clear dose-response relationship has not been established. Tea-derived catechins and polymers are being intensively studied as components of functional foods, because the results of epidemiologic, *in vitro* and animal research indicate little toxicity and great potential benefit in preventing cancer or treating inflammation-associated disorders. Clinical trials have shown a mild cholesterol-lowering effect and perhaps some benefit for enhancing weight loss.

PROBIOTICS AND PREBIOTICS

Probiotics are live microbes that exert health benefits when ingested in sufficient quantities. Species of *Lactobacilli* and *Bifidobacteria*, sometimes combined with *Streptococcus thermophilus* are the main bacteria used as probiotics in fermented dairy products. Most probiotic research has been done with nutraceutical preparations, but yogurt has been shown to alleviate lactose intolerance, prevent vaginal candidosis in women with recurrent vaginitis and reduce the incidence or severity of gastrointestinal infections.

Prebiotics are non-digestible food ingredients that stimulate the growth or modify the metabolic activity of intestinal bacterial species that have the potential to improve the health of their human host. Criteria associated with the notion that a food ingredient should be classified as a prebiotic are that it remains undigested and unabsorbed as it passes through the upper part of the gastrointestinal tract and is a selective substrate for the growth of specific strains of beneficial bacteria (usually *Lactobacilli* or *Bifidobacteria*), rather than for all colonic bacteria, inducing intestinal or systemic effects through bacterial fermentation products that are beneficial to host health. Prebiotic food ingredients include bran, psyllium husk, resistant (high amylose) starch, inulin (a polymer of fructofuranose), lactulose, and various natural or synthetic oligosaccharides, which consist of short chain complexes of sucrose, galactose, fructose, galactose, glucose, maltose or xylose. The best known effect of prebiotics is to increase fecal water content, relieving constipation. Bacterial fermentation of prebiotics yields short-chain fatty acids (SCFA) that nourish and encourage differentiation of colonic epithelial cells. Absorbed SCFA decrease hepatic cholesterol synthesis. Fructooligosaccharides (FOS) have been shown to alter fecal biomarkers (pH and the concentration of bacterial enzymes like nitroreductase and beta-glucuronidase) in a direction that may convey protection against the development of colon cancer.

Several prebiotics have documented effects that are probably independent of their effects on gastrointestinal flora. Whereas the high phytic acid content of bran inhibits the absorption of minerals, FOS have been shown to increase absorption of calcium and magnesium. Short chain FOS are sweet enough to be used as sugar substitutes. Because they are not hydrolyzed in the mouth or upper GI tract, they are non-cariogenic and non-insulogenic. Bran contains immunostimulating polysaccharides, especially beta-glucans and inositol phosphates, which have been shown to stimulate macrophage and natural killer cell activity *in vitro* and in rodent experiments. The poor solubility and absorption of beta-glucans and inositol phosphates are significant barriers to clinical effects in humans.

IMMUNE MODULATORS

Several substances produced by animals and fungi have been investigated for immune modulating effects. Fish oils are the most studied. As a source of omega-3 fatty acids, fish oil consumption by humans has been shown to influence the synthesis of inflammatory signaling molecules like prostaglandins, leukotrienes and cytokines. In addition to direct effects on prostanoid synthesis, omega-3 fats have also been shown to directly alter the intracellular availability of free calcium ions, the function of ion channels and the activity of protein kinases. Generally administered as nutraceuticals rather than as functional foods, fish oil supplements have demonstrated anti-inflammatory and immune suppressive effects in human adults. A high intake of the omega-3 fatty acids, eicosapentaenoic (EPA) and docosahexaenoic (DHA), from seafood or fish oil supplements has also been associated with prevention of several types of cancer, myocardial infarction, ventricular arrhythmias, migraine headaches, and premature births, and with improved control of type 2 diabetes mellitus, inflammatory bowel disease, rheumatoid arthritis, cystic fibrosis, multiple sclerosis, bipolar disorder and schizophrenia. EPA but not DHA is effective for schizophrenia and depression; DHA but not EPA improves control of blood sugar in diabetics. The benefits of fish oil supplements have prompted efforts at increasing the omega-3 content of common foods by adding fish oil or flax oil extracts. Consumption of these has been associated with decreased levels of some inflammatory biomarkers, including thromboxane B2, prostaglandin E2 and interleukin 1-beta.

Feeding flax seed meal or fish meal to hens enriches the omega-3 content of the yolks of the eggs they lay. Consumption of these omega-3 eggs increases the omega-3 content of plasma and cellular phospholipids and produces an improved blood lipid profile when compared with consumption of standard eggs. Egg yolk is not only a source of fatty acids, but also of carotenoids and immunoglobulins. The xanthophyll carotenoids zeaxanthin and its stereoisomer lutein are readily absorbed from egg yolk. Their consumption is associated with a decreased incidence of macular degeneration and cataract. Immunizing hens to specific pathogens and extracting the antibodies present in their egg yolks yields a functional food that has been shown to prevent enteric bacterial or viral infection in experimental animals.

Bovine colostrum, the milk produced by cows during the first few days post-partum, has a long history of use as a functional food. Compared to mature milk, colostrum contains higher amounts of immunoglobulins, growth factors, cytokines, and various antimicrobial and immune-regulating factors. Consumption of bovine colostrum has been shown to reduce the incidence of diarrheal disease in infants and of symptoms of respiratory infection in adults. Specific hyperimmune bovine colostrums, produced by immunizing cows to pathogenic organisms like *Cryptosporidium parvum*, *Helicobacter. pylori*, rotavirus, and *Shigella* spp., may prevent or treat infection by these organisms. Human studies have also shown that consumption of bovine colostrum can improve anaerobic athletic performance and prevent the enteropathy induced by use of non-steroidal anti-inflammatory drugs.

Mushrooms play a major role in traditional Chinese medicine and as components of contemporary Chinese health foods. Many *Basidiomycetes* mushrooms contain biologically active polysaccharides in fruiting bodies, cultured mycelium, or culture broth. Most belong to the group of beta-glucans that have both beta-(1-->3) and beta-(1-->6) linkages. Although they stimulate macrophages and natural killer cells, the anti-cancer effect of mushroom polysaccharide extracts appears to be mediated by thymus-derived lymphocytes. In experimental animals, mushroom polysaccharides prevent oncogenesis, show direct antitumor activity against various cancers, and prevent tumor metastasis. Clinical trials in humans have shown improvement in clinical outcome when chemotherapy was combined with the use of commercial mushroom polysaccharides like lentinan (from *Lentinus edodes* or shiitake), krestin (from *Coriolus versicolor*) or schizophyllan (from *Schizophyllum commune*). Mushroom extracts may fulfill their potential more as medicines than as functional foods.

DESIGNER FOODS

An important direction in the development of functional foods is the combination of numerous ingredients to achieve a specific set of goals, rather than efforts to uncover the potential benefits of a single food source. Infant formula was probably the first area for designer foods of this type, because of the profound influence of nutrients on the developing brain and immune system. The addition of DHA to infant formula for enhancing brain and visual development, the alteration of allergenic components in food and the possible use of probiotics and nucleotides to enhance immune response are important developments in this area.

Sports nutrition is another established arena for designer foods. Specific nutritional measures and dietary interventions have been devised to support athletic performance and recuperation. Oral rehydration products for athletes were one of the first categories of functional foods for which scientific evidence of benefit was obtained. Oral rehydration solutions must permit rapid gastric emptying and enteral absorption, improved fluid retention and thermal regulation, to enhance physical performance and delay fatigue. Carbohydrates with relatively high glycemic index combined with whey protein concentrates or other sources of branched chain amino acids have been shown to enhance recovery of athletes. Caffeine, creatine, ribose, citrulline, L-carnitine and branched chain amino acids have each been shown to improve exercise performance or diminish post-exercise fatigue. Whether combinations of these ingredients, blended into foods or beverages, will perform better than the individual ingredients will help to determine the design of future sports foods.

Optimal cardiovascular health involves prevention of excessive levels of oxidant stress, circulating homocysteine, cholesterol, triglycerides and fibrinogen, and protection of the vascular endothelium. A mix of ingredients that may supply all of these effects could consist of soy protein powder, oat beta-glucan, plant sterols and stanols, folic acid, L-arginine, DHA, magnesium, and red wine or green tea polyphenols. Evidence suggests that addressing multiple nutritional influences on cardiovascular health will be more beneficial than addressing only one influence, but more definitive studies are needed. Genetic factors may need to be incorporated for designer foods to achieve their full potential. Polyunsaturated fatty acids, for example, raise the serum concentration of HDL-cholesterol among individuals who carry the Apo A1-75A gene polymorphism, but reduce HDL-cholesterol levels of individuals who carry the more common Apo A1-75G polymorphism.

RECOMMEDNED READING

Ashwell, M. (2001). Functional Foods: A Simple Scheme for Establishing the Scientific Basis for all Claims. *Public Health Nutrition*. CABI Publishing, Oxford, UK, **4**(3):859–862.

Bellisle, F., Diplock, A.T., Hornstra, G., Koletzko, B., Roberfroid, M.B., *et al*., eds. (1998). Functional Food Science in Europe. *British Journal of Nutrition*. CABI Publishing, Oxford, UK, **80**(Suppl.1):S1–S193.

Clydesdale, F. M., and Chan, S. H., eds (1995), First International Conference on east-West Persepctives on Functional Foods, *Nutrition Reviews*, 54 (11, part II): S1-S202.

Diplock, A.T., Aggett, P.J., Ashwell, M, Bornet, F., Fern, E.B., Roberfroid, M.B., eds. (1999). Scientific Concepts of Functional Foods in Europe: Consensus Document. *British Journal of Nutrition*. CABI Publishing, Oxford, UK, **81**(Suppl.):S1–S27.

Farnworth, E.R., *Handbook of Fermented Functional Foods (2003) CRC Press, USA*

Goldberg, I., editor (1994) *Functional Foods Designer Food, Pharmafoods, Nutraceuticals,* Chapman and Hall, New York

ILSI North America Technical Committee on Food Components for Health Promotion (1999). Food Component Report. ILSI Press, Washington, DC, USA.

Knorr, D. (1999). Technology Aspects Related to Microorganisms in Functional Food. *Trends in Food Science and Technology.* Elsevier Science, UK, **9**(8-9, Special Issue):295–306.

Langseth, L. (1995). Oxidants, Antioxidants and Disease Prevention. *ILSI Europe Concise Monograph Series.* ILSI Press, Washington, DC, USA.

Langseth, L. (1996). Nutritional Epidemiology: Possibilities and Limitations. *ILSI Europe ConciseMonograph Series.* ILSI Press, Washington, DC, USA..

Langseth, L. (1999). Nutrition and Immunity in Man. *ILSI Europe Concise Monograph Series.* ILSI Press, Washington,DC, USA..

Meskin, M.S., Biidlack B.I., Davies, A.J., Omaye, S.T., eds (2002)*Phytochemicals in Nutrition and Healt,* CRC Press, USA

Roberfroid, M.B. (2000). Defining Functional Foods. In: Gibson, G. and Williams, C., eds. *Functional Foods.* Woodhead Publishing Ltd., Cambridge, UK.

Truswell, A.S. (1995). Dietary Fat: Some Aspects of Nutrition and Health and Product Development. *ILSI Europe Concise Monograph Series.* ILSI Press, Washington, DC, USA.

Table 1.

Some ingredients conferring FOSHU status on Japanese functional foods

Ingredient	Physiological function
Dietary fiber	Improve gastrointestinal function
psyllium seed husk	
wheat bran	
hydrolyzed guar gum	
Oligosaccharides	Improve gastrointestinal function and mineral absorption
xylo-, fructo-, isomalto-	
soy-derived	
polydextrose	
Bacterial cultures	Improve gastrointestinal function
Lactobacilli	
Bifidobacteria	
Soy protein isolates	Reduce cholesterol levels
Diacylglycerols	Reduce triglyceride levels
Sugar alcohols	Prevent dental caries
maltitol	
palatinose	
erythritol	
Green tea polyphenols	Prevent dental caries
Absorbable calcium	Improve bone health
calcium citrate malate	
casein phosphopeptide	
Heme iron	Correct iron deficiency
Eucommiacea (tochu) leaf glycosides	Reduce blood pressure
Lactosucrose, lactulose, indigestible dextrin	Improve gastrointestinal function

Table 2.
Phytochemicals Associated with Health Promotion and Disease Prevention

Group	Typical components	Biological activities	Food sources
Carotenoids	alpha- and beta-carotene cryptoxanthin, lutein, lycopene, zeaxanthin	Quench singlet and triplet oxygen, increase cell-cell communication	Red, orange and yellow fruits and vegetables, egg yolk, butter fat, margarine
Glucosinolates,	indole-3-carbinol	Increase xenobiotic	Cruciferous
Isothiocyanates	sulphoraphane	metabolism, alter estrogen metabolism	vegetables, horseradish
Inositol phosphates	inositol hexaphosphate (phytate)	Stimulate natural killer cell function, chelate divalent cations	Bran, soy foods
Isoflavones	genistein, daidzein	Estrogen agonist and antagonist, induce apoptosis	Soy foods, kudzu
Lignans	enterolactone, enterolactone	Estrogen agonists and antagonists, inhibit tyrosine kinase	Flax seed, rye
Phenolic acids	gallic, ellagic, ferulic, chlorogenic, coumaric	Antioxidant, enhance xenobiotic metabolism	Diverse fruits, vegetables
Phytoallexins	resveratrol	Antioxidant, platelet inhibition, induce	Red wine, grape seed

		apoptosis	
Polyphenols	flavonoids, chalcones, catechins, anthocyanins, proanthocyanidins	Antioxidant, enhance xenobiotic metabolism, inhibit numerous enzymes	Diverse fruits, vegetables, red wine, tea
Saponins	glycyrrhizin, ginsenosides	Antimicrobial, immune boosting, cytotoxic to cancer cells	Legumes, nuts, herbs
Sterols	beta-sistosterol, campestrol	Bind cholesterol, decrease colonic cell proliferation, stimulate T-helper-1 cells	Nuts, seeds, legumes, cereal grains
Sulfides	diallyl sulfides	Antimicrobial, antioxidant	Garlic, onions