Multi-functional foods

Koji Yamada*

Department of Applied Microbial Technology, Faculty of Biotechnology and Life Sciences, Sojo University, PhD, Kumamoto, Japan

Abstract

Foods contain various biologically active substances. They exert various activities and some of them exert plural functions [1]. Thus, foods are basically multifunctional. However, contents and composition of these functional factors are fairly different with foods. Therefore, we have to take various foods to maintain our health. On the other hand, unbalanced diet may leads to the occurrence of various food style dependent diseases. To avoid such diseases, it is important to produce and afford nutritionally balanced foods.In addition, excess intake of energy and some food components induce such diseases. Among food components, excess intake of lipids, especially unsaturated fatty acids, induces various diseases. To avoid induction of such diseases, it is necessary to produce and afford multi-functional foods which prevent various diseases simultaneously. Fortunately, we can utilize multifunctional factors to produce multifunctional foods.

Keywords: Dietary fibers, Multifunctional foods, Anti-oxidative activity.

Accepted on 10 October, 2017

B Dietary fibers (DF) is a typical multifunctional factor presents in various plant foods and used for production of healthy foods in various countries. Though oxidized products of unsaturated fatty acids induce various diseases, they can also inhibit the occurrence of other diseases. Thus, the addition of antioxidants is important to utilize the abilities of unsaturated fatty acids. Since antioxidants suppress the oxidation of unsaturated fatty acids, they can suppress the expression of their many inconvenient effects. In addition, antioxidants exert multifunctional effects independent with their anti-oxidative activity. Effective use of these multifunctional factors may greatly enhance the ability of multifunctional foods.

In the designing of multi-functional foods, maintenance of safety is very important. Highly effective functional factors often induce side effects when they were taken excessively. To enhance the safety of multi-functional foods, simultaneous uses of biologically active factors may be effective. Some multifunctional factors are reported to have synergic effects. For example, simultaneous use of a-tocoferal and sesamin exert their biological effect at lower doses. Such decrease of dosage may attribute to the maintenance of safety of multifunctional foods, as well as reduction of production cost.

Biologically Active Food Components

Biologically active food components are given below (Table 1).

Table 1: Biologically active food components.

Food components		Functions
Saccharides	Monosaccharides	Glucose is a major energy source of body, especially of brain. Fructose and galactose are also available for energy source. Sugar alcohols are hardly absorbable, and used as low-calorie sweetener.
	Oligosaccharides	Digestive ones such as sucrose are utilized as an energy source. Hardly digestive ones are used as low-calorie sweetener. Some of them enhance the growth of lactic acid bacteria.
	Polysaccharides	Digestive ones such as starch are utilized for energy source. Hardly digestive ones called dietary fibers exert various biological effects.
Proteins	Amino acids	Essential amino acids should be taken from foods. Nonessential amino acids can be synthesized via TCA cycle. These amino acids can be converted to various biologically substances such as nucleic acid bases via TCA cycle
	Peptides	Degraded products of proteins. Some of them exert biological activities such as enhancement of mineral absorption, inhibition of blood pressure elevation, anti-oxidative activity etc.
	Proteins	Digestive ones afford essential and nonessential amino acids. Some of hardly digestive one act as dietary fibers. Most functional proteins lose their activities through their digestion. The ones exert their activities in the digestive truck such as digestive enzymes are useful for our health.

Lipids	Fatty acids	They are composed of saturated and unsaturated fatty acids. The former divided into 3 groups, such as short-chain, medium-chain, and long-chain fatty acids. Short-chain fatty acids enhance excretion of feces and middle-chain fatty acids are effective energy source of digestive tract disease patients. Long chain fatty acids are classified into n-3, n-6, and n-9 groups depending on the position of the first double bond counted from methyl end. They exert various biological effects, varying with groups.
	Neutral lipids	The one glycerol is bound to 3 fatty acids. Their functions are different with fatty acid composition.
	Phospholipids	The one glycerol is bound to 2 fatty acids and one basic component. Main component of cell membrane. Their functions are different with fatty acid composition.
	Lipid soluble components	Cholesterol is important as a component of cell membrane and a starting material of bile acid synthesis. Increase of serum cholesterol level leads to the occurrence of circulatory disease.
Vitamins	Water-soluble	Vitamin Bs and C. The former is important for the regulation of metabolism. The latter is essential for collagen synthesis and exerts anti-oxidative activity.
	Lipid-soluble	Vitamins A, E, D and K. Vitamin E effectively suppress oxidation of unsaturated fatty acids especially lipic circumstance such as cell membrane
Others	Minerals	Ca is important for maintenance of bones and teeth. Fe is essential for the transport of oxygen. K is useful for the decrease of blood pressure. Some of minerals regulate the metabolism as co-factors of various enzymes.
	Antioxidants	The components with anti-oxidative activity.

As summarized in Table 1, foods contain various biologically active substances. Digestive polysaccharides and sugars are important energy source for animals. However, persistent elevation of serum glucose level lead to the occurrence of diabetes. On the other hand, hardly digestible polysaccharides suppress the degradation of digestive polysaccharides and incorporation of glucose. This leads to the prevention of diabetes.

In addition, hardly digestive polysaccharides can bind lipid-soluble components such as carcinogenic components and lipids. This leads to the expression of anti-cancer and lipid-metabolism improving activities. Thus, hardly digestive polysaccharides are called DF and widely used for the production of health-oriented foods. Some oligosaccharides are also hardly digestive. In addition, such oligosaccharides enhance the growth Lactobacillus and Bifidus bacteria which improve the circumstance of gut. Thus, these saccharides are widely used as low-calorie biologically active components.

Proteins are polymers composed of about 20 amino acids. Since human cannot synthesis some amino acids sufficiently, they are called essential fatty acids (EFA) which should be taken from various foods. Balanced intake of EFA is important to keep health, because they are necessary for in vivo synthesis of various regulatory proteins.

Food proteins are digested to peptide or amino acids in the digestive truck and incorporated into our body. Some peptides are reported to exert biological effects such as enhancement of Ca absorption and inhibition of angeotensin-inducing enzyme activity. The former is useful for the prevention of osteoporosis and the latter for the inhibition of blood pressure elevation.

Lipids are lipid-soluble components present in foods. Major component is neutral lipid in which glycerol is bound to three fatty acids. The function of neutral lipid is highly dependent on the composition of fatty acids. Animal fats are rich in saturated fatty acids and oleic acid (OA18:1n-9). Most plant oils are rich in polyunsaturated fatty acids (PUFA) belongs to n-6 series. On the other hand, fish oils are rich in PUFA belongs to n-3 series.

PUFA with 20 carbons were oxidized by lipoxygenase or cyclooxigenase to give various eicosanoids which have diverse biological effects. Leucotrienes (LT) produced from arachidonic acid (AA, 20:4n-6) are one of inducers of food allergy, but the activity of LT produced from eicosapentaenoic acid (EPA, 20:5n-3) is very low. In addition, EPA-derived LT suppress the expression of allergic effect of AA-derived LT, through a competition with AA-derived LT. Thus, the composition of PUFA in diets is highly important in the prevention of food allergy.

PUFA is easily oxidized in vivo and the oxidized products induce various diseases. To prevent the oxidation of PUFA in vivo, intake of antioxidants is important. Vitamins are low molecular regulatory factors present in various foods, and balanced intake of vitamins is important to maintain healthy condition. Among them, vitamin E is a lipid-soluble antioxidant which efficiently suppresses the oxidation of unsaturated fatty acids in lipophilic circumstance such as cell membrane.

On the other hand, vitamin C is a water-soluble antioxidant which is effective in the prevention of oxidation in foods or in body fluids. In addition, various types of antioxidants are present in foods. These antioxidants prevent the occurrence of food-style depending diseases via suppression of oxidation of unsaturated fatty acids. In addition, some antioxidants induce various biological effect independent with their anti-oxidative activity. This means that antioxidants are important multi-functional factors as well as DF and PUFA.

Multifunctional activity of dietary fats

Typical multifunctional factors in foodstuffs are given below (Table 2).

Table 2: Typical multifunctional factors in foodstuffs.

Food components	Chracteristics
Dietary fibers	Water-insoluble ones are non-digestive. Cellulose, hemicellulose and lignins are plant cell wall components. Chitin is a polymer of N-acetyl glucosamine isolated from shells of crustacean. Deacetylated chitin (chitosan) is acid-soluble. Intestinal regulation, anti-cancer, anti-lipidemia, and anti-diabetes. Water-soluble ones are partially digestive and give smaller calories than digestive polysaccharides. Glucomannan, and fructomannan are present in vegetables, and pectin in fruits. Gums isolated from various plants (Arabia gum, karaya gum, tragacan gum, locust bean gum and guar gum), sea weed polysaccharides (agarose, arginic acid, carageenan) and bacterial products (xysanthan gum and prulan) are also used in food industries. In addition to the effects of water-insoluble DF, they exert strong immunoreguratory effects.
Fatty acids	Oleic acid (OA, 18:1n-9) is a representative monoenic fatty acid, which enhances growth of mammalian cells. Since it can be produced from a saturated fatty acid rich in animal tissue, it is not essential. Animal cell cannot introduce second double bond in monoenic fatty acids. Thus, polyunsaturated fatty acids (PUFA) should be taken from plant foods. Linoleic acid (LA, 18:2n-6) is a starting material of n-6 series PUFA synthesis and metabolized to g-linolenic (GLA, 18:3n-6), dihomo- γ-linolenic (DGLA, 20:3n-6), arachidonic (AA, 20:4n-6) acids. DGLA and AA are further metabolized to eicosanoids which exert various biological effects. PUFA belong to n-3 series such as eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic (DHA, 22:6n-3) are metabolized from α-linolenic acid (ALA, 18:3n-3). EPA is further metabolized to eicosanoids which exert various biological effects.
Antioxidants	It composed from various compounds with anti-oxidative activity. Some of polyphenols with more than two OH groups in benzene ring exert a strong anti-oxidative activity. Catechins are antioxidants rich in green tea and exert diverse biological effects such as anti-cancer, anti-allergic and anti-obesity effects. Flavonoids (flavon, flavonol, antocyan) are antioxidants present in vegetable and fruits. In addition, various foods contain various nonpolyphenolic antioxidants.

Most popular multifunctional factor is DF. DF is polysaccharides which are not digestive or hardly digestive by human digestive enzymes. Some of them are water-insoluble and the others are water-soluble. Typical water-insoluble DF is cellulose. Because of its hydrophobic surface, it adsorbs lipophilic food components, such as dietary fats or carcinogenic compounds. Since DF cannot be absorbed in our body, it inhibits the absorption of these lipophilic components. This leads to the expression of its lipid metabolism regulating and anti-cancer activities.

On the other hand, water-soluble DF (WSDF) is partially digested by intestinal bacteria to give short-chain fatty acids (SCFA), such as acetic, propionic and butyric acids. Since acetic acid is absorbed at intestinal wall and used as an energy source, WSDF afford some amounts of energy. On the contrary other SCFA exert some physiological activities. For example, butyric acid arrests the cell cycle of diploid mammalian cells at both G1 and G2 phases, and the cells arrested at the G2 phase rapidly converted to tetraploid G1 cells [2]. This leads to the production of polyploid cells with a high efficiency [3]. On the other hand, the cells transformed with oncogenes are hardly arrested to the G2 phase by butyric acid and the cells passed G2 phase lose viability quickly. This leads to the expression of its anti-cancer effects [4].

In addition, WSDF can express lipid metabolism regulating and anti-cancer activities simultaneously, since they have lipophilic part on their surface as well as water-insoluble DF. We tried to clarify the difference in physiological activities between two types of DF and found that WSDF exert much stronger immuno-regulatory activity than cellulose [1]. Among WSDF, the rats fed glucomannan (GM) or pectin (P) gave higher serum IgA and IgG levels and a lower serum IgE level than those fed cellulose.

In the feeding experiments, lipid metabolism regulating activity of food components can be assayed, simultaneously with immuno-regulatory activity. The rats fed WSDF such as guar gum (GG), GM or P gave lower serum cholesterol and triglyceride levels than those fed cellulose, when aged eight-month-old Sprague-Dawley (SD) rats were fed the diets containing the above DFs for 3 weeks [5]. On the other hand, these results were not obtained in 8-month old aged SD rats [6]. This suggests that the dietary effects of WSDF are age-dependent. Similarly, the young SD rats fed GG, GM or P gave significantly higher serum IgA levels than those fed cellulose, but the effect was not observed in aged rats.

In the feeding experiments, lymphocytes were isolated from spleen and mesenteric lymph node (MLN), and cultured for 24 h in the absence of DF to determine the effect on Ig productivity of these lymphocytes In this experiment, lymphocytes isolated from MLN of young SD rats fed WSDF gave higher IgA, IgG, and IgM productivities than those isolated from the rats fed cellulose.

In the case of splenocytes, the stimulating effects were weaker than those observed in MLN. In aged rats, the stimulating effect was observed only in MLN lymphocytes, but not in splenocytes. These results suggest that the feeding effect of WSDF is dependent on immune tissue, as well as age of rats.

As shown above, feeding experiments using experimental animals afford an excellent system to study multi-functional activity of food components. When some biological effects were observed in animal experiment, cultured cells are often used to clarify the regulatory mechanism food components. However, the in vitro system was not effective in WSDF. When established cells or lymphocytes with Ig-producing activity were cultured in the presence of WSDF or SCFA, such changes in Ig productivity were not induced. This suggests that the effect of WSDF was not induced through the direct interaction of WSDF with immune cells.

Multi-functional activity of polyunsaturated fatty acids

Biological activities of unsaturated fatty acids are dependent on their structures. Linoleic acid (18:2n-6) has a double bond at the 6th position from its methyl terminal and metabolized to dihomo-γ-linolenic acid (20:3n-6) and finally to arachidonic acid (AA, 20:4n-6) *via* γ-linolenic acid (18:3n-6) and dihomo-g-linoleic acid (20:3n-6). The AA in membrane phospholipids (PL) is cut out by phopholipase and then oxidized with lipoxygenase to 4-series leucotrienes (LT) which induce type I allergy. On the other hand, α-linolenic acid (18:3n-3) has a double bond at the 3rd position from its methyl terminal and metabolized to eicosapentaenoic (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3). EPA is also oxidized with lipoxygenase to 5-series LT's which suppress type I allergy. Since n-3 PUFAs can be substituted with AA in membrane PL, they can suppress allergic reaction through the reduction of membrane AA level.

In addition, dietary n-3 PUFAs decreased serum triglyceride and cholesterol levels [7]. The lipid metabolism-regulating activity can be observed in the rats fed fish oils rich in EPA or DHA, as well as the above immuno-regulatory effects [8]. The fish oils with different EPA and DHA contents can be prepared by mixing some fish oils, but it is impossible to prepare the fish oil containing solely EPA or DHA, because all fish oils contain both components. To clarify the difference of biological activity between EPA and DHA, we used purified EPA and DHA esters in the feeding experiment and found that EPA ester exerted stronger anti-allergic effect than DHA esters, as expected [9].

In addition, conjugated linoleic acid (CLA) exerts multifunctional effect, such as anti-cancer [10], lipid metabolism-regulating [11], and immune-regulatory activities [12].CLA is a generic term for the positional and geometric isomer of linoleic acid (LA, 18:2n-6). LA is converted to CLA by intestinal bacteria and small amount of CLA is detected in dairy products. The naturally produced CLA has 9cis, 11trans (9c, 11t) conformation. On the other hand, 10trans, 12 cis (10t, 12c) CLA is produced at the similar level with 9c, 11t CLA, when LA is heated in alkaline solution. Among them, 10t, 12c CLA exerts much stronger biological effects than 9c, 11t CLA. This means that the artificially produced CLA is more excellent effecter than naturally produced CLA. To use the artificial product for human health improvement, confirmation of safety is essential.

Multi-functional activity of antioxidants

There are various types of natural and synthesized antioxidants which are used for the inhibition of oxidation of food component in vitro or in vivo. They exert various physiological activities in addition to the anti-oxidative activity. Among them, biological effects of polyphenolic compounds were widely studied. Diphenols with two OH groups on a benzene ring at ortho or para position exert strong anti-oxidative activity, as well as anti-allergic effect [13,14]. These polyphenols may exert the activities through the binding to cell surface or through the interaction with intracellular components after their incorporation into cells. In general, triphenol compounds exert stronger activity than diphenol compounds on cell surface [13,14] probably due to stronger interaction with cell surface [15].

Among tea polyphenols, epigallocatechin gallate (EGCg) with 2 triphenol groups exerts strong biological activities. For example, it exerts much stronger toxicity against rat 3Y1 diploid fibroblasts transformed by E1A than other tea polyphenols, but their toxicities against normal 3Y1 cells are unchanged [16]. This means that EGCg is more effective anti-cancer compound with low toxicity against normal cells than other catechins. Since it strongly suppresses both histamine and LTB4 release from rat peritoneal exudates cells stimulated with a calcium ionophore A23187 [14], EGCg may also be useful for prevention of type I allergy.

In the case of vitamin E derivatives, clarification of their tissue distribution is important [17]. Tocopherol (Toc) derivatives are distributed to various tissues, but the presence of tocotrienol (T3) derivatives is limited in several tissues. When a mixture of Toc and T3 is administrated into the stomach of SD rats and their tissue contents are determined after around 16-hr fasting, T3 can be detected only in small number of tissues. On the other hand, T3 derivatives are detected in various tissues, when their tissue levels are determined without fasting. Though α-Toc is detected in various tissues and the levels are fairly stable, the levels of α-T3 and γ-T3 are usually much lower than that of α-Toc. In the adipose tissues, small amounts of α-T3 and γ-T3 are detected at 0 hr and the levels are increased with the elongation of ingestion time.

Detection of T3 derivatives without T3 administration and the increase of T3 levels after T3 administration suggest that T3 derivatives are accumulative in the adipose tissues. In other tissues, T3 derivatives are not detectable at 0 h and accumulated with the elongation of ingestion time in some tissues. In the liver and MLN, the levels of T3 derivatives were highest at 8 hr after ingestion and decreased at 24 h.

In these tissues, T3 may be incorporated quickly and then released or metabolized thereafter. The quickness of disappearance in some tissues may be the reason why T3's is detectable only in limited tissues. T3 derivatives often exert stronger biological effects than Toc derivative in cell culture assays [18]. However, such biological effects cannot be expressed in the tissues where T3 are not present. Thus, clarification of tissue distribution is essential for the determination of target tissue of biologically active substances.

Design of multi-functional foods

Some biologically active substances interact with other substances. For example, two anti-oxidative components, such as α-Toc and sesamin, exert a synergic effect [19]. When rats were fed these compounds simultaneously, these components exert anti-allergic effects at the doses where each component exerts no activity. In addition, tea polyphenol administration enhances the anti-allergic effect of n-3 PUFA. Though LTB4 productivity of peritoneal exudates cells isolated from the rats fed perilla oil rich in n-3 PUFA was significantly lower than that from the rats fed safflower oil rich in n-6 PUFA, administration tea polyphenol further decreaced LTB4 of the cells [20]. In the case of EGCg, coexistence of phosphodiesterase inhibitor strongly enhanced the expression of its biological activity [21]. Such combinational use of biologically active components allows us to decrease the dose of these components [22]. This leads to the improvement of safety and reduction production costs. Thus, the studies on the interaction of biologically active substances are also important to produce multifunctional foods with a high safety.

References

1. Lim BO, Yamada K, Nonaka M, et al. Dietary fibers modulate indices of intestinal immune function in rats. J Nutr. 1997;127:663-7.
2. Yamada K, Kimura G. Formation of proliferative tetraploid cells after treatment of diploid cells with sodium butyrate in rat 3Y1 fibroblasts. J Cell Physiol. 1985;122:59-63.
3. Yamada K, Ohtsu M, Kimura G. Isolation of tetraploid clones with high efficiency from diploid 3Y1 rat fibrloblasts. Develop Biol Animal. 1985;22:212-6.
4. Yamada K, Ohtsu M, Sugano M, et al. Effect of butyrate on cell cycle progression and polyploidization of various types of mammalian cells. Biosci Biotechnol Biochem. 1992;56:1261-5.
5. Yamada K, Tokunaga Y, Ikeda A, et al. Dietary effect of guar gum and its partially hydrolyzed product on lipid metabolism and immune function of Sprague-Dawley rats. Biosci Biotechnol Biochem. 1999;63:2163-7.
6. Yamada K, Tokunaga Y, Ikeda A, et al. Effect of dietary fiber on the lipid metabolism and immune function of aged Sprague-Dawley rats. Biosci Biotechnol Biochem. 2003;67:429-33.
7. Huglund O, Luostarinen R, Wallin R, et al. The effect of fish oil on triglycerides, cholesterol, fibrinogen and malonyldialdehyde in humans supplemented vitamin. Eur J Nutr. 1991;121:163-9.
8. Hung P, Kaku S, Yunoki S, et al. Dietary effect of EPA-rich and DHA-rich fish oils on the immune function of Sprague-Dawley rats. Biosci Biotechnol Biochem. 1999;63:135-40.
9. Hung P, Gu JY, Kaku S, et al. Dietary effect of eicosapentaenoic and docosahexaenoic acid esters on lipid metabolism and immune parameters in Sprague-Dawley rats. Biosci Biotechnol Biochem. 2000;64:2588-93.
10. Yamasaki M, Chujo H, Koga Y, et al. Potent cytotoxic effect of trans-10, cis12 isomer of conjugated linoleic acid on rat hepatoma dRLh-84 cells. Cancer Lett. 2002;188:171-80.
11. Yamasaki M, Ikeda A, Oji M, et al. Modulation of body fat and serum leptin levels by dietary conjugated linoleic acid in Sprague-Dawley rats fed various fat-level diets. Nutrition. 2003;19:30-5.
12. Yamasaki M, Kitagawa T, Chujo H, et al. Physiological difference between free and triglyceride-type conjugated linoleic acid on the immune function of C57BL/6N mice. J Agric Food Chem. 2004;52:3644-8.
13. Yamada K, Tachibana H, Matsuo N, et al. Structure-activity relationship of immunoregulatory factors in foodstuffs. Food Sci Technol Res. 1999;5:1-8.
14. Yamada K, Mori K, Ueyama T, et al. Structure-activity relationship of polyphenols on inhibition of chemical mediator release from rat peritoneal exudate cells. In Vitro Cell Develop Biol Animal. 1999;35:169-74.
15. Yano S, Fujimura Y, Umeda D, et al. Relationship between the biological activities of methylated derivatives of (-)-epigallocatechin-3-O-gallate (EGCG) and their cell surface binding activities. J Agric Biol Chem. 2007;55:7144-8.
16. Yamada K, Mitsui T, Okuda A, et al. Cytotoxic and cytostatic effect of polyphenols against rat 3Y1 fibroblasts transformed by E1A gene of human adenovirus type 12. Int J Oncology. 1993;2:89-93.
17. Okabe M, Oji M, Ikeda I, et al. Tocotrienol levels in various tissues of Sprague-Dawley rats after intragastric administration of tocotrienol. Biosci Biotechnol Biochem. 2002;66:1768-71.
18. Sakai M, Okabe M, Yamada K, et al. Apoptosis induction by □-tocotrienol in human hepatoma Hep3B cells. J Nutr Biochem. 2006;17:672-6.
19. Gu JY, Nonaka M, Yamada K, et al. Effect of sesamin and □-tocopherol on the production of chemical mediators and immunoglobulins in Brown-Norway rats. Biosci Biotechnol Biochem. 1994;58:1855-8.
20. Matsuo N, Yamada K, Mori M, et al. Inhibition by dietary tea polyphenols of chemical mediator release from rat peritoneal exudate cells. Biosci Biotechnol Biochem. 2000;64:1437-43.
21. Kumazoe M, Kim Y, Bae JH, et al. Phosphodiesterase inhibitor 5 act as a potent agent sensitizing acute myeloid leukemia cells to 67-kDa laminin receptor-dependent apoptosis. FEBS Lett. 2013;587:3052-7.
22. Yamada K, Development of multifunctional foods. Biosci. Biotechnol. Biochem. 2017;81:849-53.

*Correspondence to

Dr. Koji Yamada

Department of Applied Microbial Technology,

Faculty of Biotechnology and Life Sciences,

Sojo University, PhD,

Kumamoto, Japan

E-mail: yamada67@bio.sojo-u.ac.jp