

Biologically Active Vitamin B₁₂ Compounds in Foods for Preventing Deficiency among Vegetarians and Elderly Subjects

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ABSTRACT: The usual dietary sources of vitamin B₁₂ are animal-source based foods, including meat, milk, eggs, fish, and shellfish, although a few plant-based foods such as certain types of dried lavers (nori) and mushrooms contain substantial and considerable amounts of vitamin B₁₂, respectively. Unexpectedly, detailed characterization of vitamin B₁₂ compounds in foods reveals the presence of various corrinoids that are inactive in humans. The majority of edible blue-green algae (cyanobacteria) and certain edible shellfish predominately contain an inactive corrinoid known as pseudovitamin B₁₂. Various factors affect the bioactivity of vitamin B₁₂ in foods. For example, vitamin B₁₂ is partially degraded and loses its biological activity during cooking and storage of foods. The intrinsic factor-mediated gastrointestinal absorption system in humans has evolved to selectively absorb active vitamin B₁₂ from naturally occurring vitamin B₁₂ compounds, including its degradation products and inactive corrinoids that are present in daily meal foods. The objective of this review is to present up-to-date information on various factors that can affect the bioactivity of vitamin B₁₂ in foods. To prevent vitamin B₁₂ deficiency in high-risk populations such as vegetarians and elderly subjects, it is necessary to identify plant-source foods that contain high levels of bioactive vitamin B₁₂ and, in conjunction, to prepare the use of crystalline vitamin B₁₂-fortified foods.

KEYWORDS: cobalamin, vitamin B₁₂ food sources, inactive corrinoids, bioactive vitamin B₁₂, vitamin B₁₂ deficiency

INTRODUCTION

Vitamin B₁₂ (B₁₂) or cyanocobalamin belongs to the group “corrinoids,” which is a group of compounds having a corrin macrocycle. B₁₂ (molecular weight = 1355.4) is stable in an aqueous solution of pH 4–7 and can be heated at 120 °C without significant loss.¹ Naturally occurring B₁₂ compounds include methylcobalamin, which functions as a coenzyme for methionine synthase (EC 2.1.1.13) involved in methionine biosynthesis, and 5'-deoxyadenosylcobalamin, which functions as a coenzyme for methylmalonyl-CoA mutase (EC 5.4.99.2) involved in amino acid and odd-chain fatty acid metabolism in mammalian cells.^{2,3} Corrinoids carrying a base other than 5,6-dimethylbenzimidazole as the lower ligand (cobalt-coordinated nucleotide) are also found in nature.

B₁₂ is synthesized only by certain bacteria⁴ and is primarily concentrated in the bodies of predators higher in the food chain. Thus, foods derived from animals, that is, meat (approximately 9.4 μg/100 g), milk (approximately 0.4 μg/100 g), eggs (approximately 1.3 μg/100 g), fish (approximately 8.9 μg/100 g), and shellfish (approximately 52.4 μg/100 g), are considered to be the major dietary sources of B₁₂.⁵ Although B₁₂ is well-known as the sole vitamin absent in plant-source foods, certain dried algae [*Porphyra* sp. (approximately 77 μg/100 g), *Chlorella* sp. (approximately 200 μg/100 g), etc.] contain substantial amounts of B₁₂.⁶ It has long been unclear whether algae have an absolute requirement for B₁₂ for growth and why algae that have no B₁₂ requirement for growth contain substantial amounts of B₁₂. However, recent biochemical and bioinformatics studies have accurately defined the B₁₂ requirements of various algae and have suggested possible physiological functions of algal B₁₂.^{7,8}

Gastrointestinal absorption of dietary B₁₂ is a complex process in humans.⁹ B₁₂ released from protein in foods is first bound to haptocorrin (salivary B₁₂-binding protein) in the stomach. After proteolysis of the haptocorrin–B₁₂ complex by pancreatic proteases in the duodenum, the B₁₂ released binds to intrinsic factor (IF; gastric B₁₂-binding protein) in the proximal ileum. The IF–B₁₂ complex can enter mucosal cells in the distal ileum by receptor-mediated endocytosis. However, it is unclear why humans require such a complex system for the gastrointestinal absorption of B₁₂ from foods.

Strict vegetarians (vegans) are at higher risk of B₁₂ deficiency than nonvegetarians.¹⁰ They must consume B₁₂-fortified foods or B₁₂-containing dietary supplements to prevent B₁₂ deficiency. Furthermore, in developing countries, childhood B₁₂ deficiency is increasing because of low consumption of animal-source foods.¹¹ Similar results have been reported among low-income populations in developed countries.¹² B₁₂ fortification of flour is considered for the high-risk population because of the high prevalence of B₁₂ deficiency worldwide.^{13,14}

A considerable proportion of elderly subjects with low serum B₁₂ levels without pernicious anemia have been recently reported to have malabsorption of protein-bound B₁₂ (food-bound B₁₂ malabsorption).¹⁵ Food-bound B₁₂ malabsorption is found in patients with certain gastric dysfunctions, such as atrophic gastritis with decreased stomach acid secretion.¹⁶ Because the bioavailability of crystalline B₁₂ is normal in patients with atrophic gastritis,

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the Institute of Medicine recommends that adults aged 51 years and older should obtain the majority of their recommended dietary allowance (RDA) of B₁₂ (2.4 μg per day for adults in the United States, Canada, and Japan) by consuming foods fortified with crystalline B₁₂ or B₁₂-containing supplements.^{17,18} The objective of this review is to present up-to-date information on various factors that can affect the bioactivity of B₁₂ in foods and identifies B₁₂-rich plant-source foods.

FACTORS AFFECTING BIOLOGICAL ACTIVITY OF B₁₂ IN FOODS

Inactive Corrinoid Compounds in Foods. *Edible Cyanobacteria.* Some species of cyanobacteria, including *Spirulina*, *Aphanizomenon*, and *Nostoc*, are produced by food and pharmaceutical industries at worldwide annual rates of 500–3000 tons.¹⁹ Tablets containing *Spirulina* sp. are sold as dietary supplements, because *Spirulina* sp. are known to contain large amounts of B₁₂.²⁰ We found that commercially available spirulina tablets contain 127–244 μg of B₁₂/100 g weight and that the values obtained by the microbiological assay method are 6–9-fold greater than those determined by the chemiluminescence method.²¹ Characterization of two corrinoid compounds from spirulina tablets identified the major (83%) and minor (17%) compounds as pseudo-B₁₂ (adeninyl cobamide) and B₁₂, respectively (Figure 1). It has been reported that pseudo-B₁₂ is

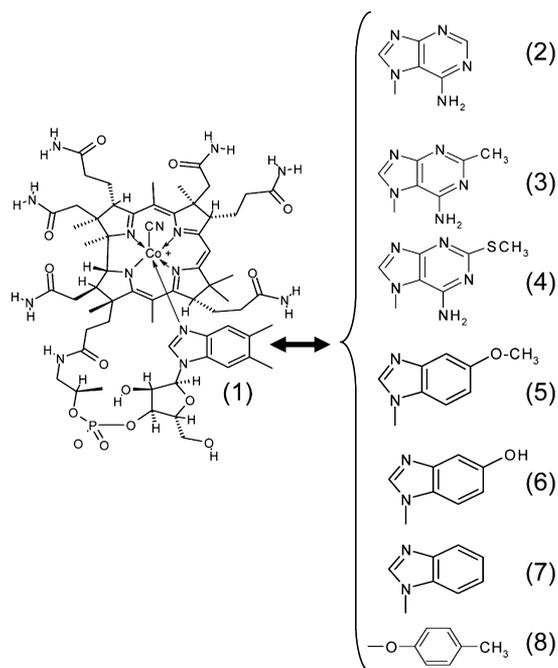


Figure 1. Structural formula of vitamin B₁₂ and partial structures of B₁₂ related compounds showing the portions that differ from vitamin B₁₂: (1) vitamin B₁₂ or cyanocobalamin; (2) pseudovitamin B₁₂ or factor IV; (3) factor A (2-methyladenylcobamide); (4) factor S (2-methylmercaptadenylcobamide); (5) factor IIIIm (5-methoxybenzimidazolylcobamide); (6) factor III (5-hydroxybenzimidazolylcobamide); (7) BIA (benzimidazolylcobamide); (8) pCC (*p*-cresolylcobamide).

barely absorbed by the mammalian intestine, and it has low affinity for IF.²² Furthermore, it has been reported that *spirulina* B₁₂ may not be bioactive in mammals.²³

All edible cyanobacteria tested, including *Aphanizomenon flos-aquae*,²⁴ *Aphanothece sacrum*,²⁵ *Nostoc commune*,²⁶ *Nostoc*

flagelliforme,²⁷ and *Nostochopsis* sp.,²⁸ contained substantial amounts of pseudo-B₁₂. These results indicate that edible cyanobacteria often contain large amounts of pseudo-B₁₂, which is known to be biologically inactive in humans.²² Therefore, cyanobacteria are not suitable for use as a source of B₁₂ for high-risk populations such as vegetarians and elderly subjects.

Edible Shellfish. Various shellfish are widely consumed by humans. Shellfish, which siphon large quantities of B₁₂-synthesizing microorganisms from seawater and fresh water, are known to be excellent sources of B₁₂.²⁹ The B₁₂-synthesizing microorganisms can also synthesize various other corrinoids, including corrinoid compounds that are inactive in humans, with different bases as the lower ligand. The B₁₂ contents of certain shellfish have been determined by the microbiological assay method to be several-fold greater than those determined by the chemiluminescence method.³⁰ When corrinoid compounds from popular shellfish such as oysters, mussels, and short-necked clams were isolated and characterized, each was identified as B₁₂.^{30,31} However, our recent study³² and unpublished data (Y. Tanioka et al.) using liquid chromatography–electrospray ionization/multistage mass spectrometry (LC/ESI-MS/MS) analysis indicated that certain edible shellfish (abalones, ark shells, corb shells, whelks, etc.) contain substantial amounts of pseudo-B₁₂, factor A, factor S, and/or factor IIIIm, as well as B₁₂ (Figure 1). Therefore, these shellfish are not adequate sources of B₁₂. Further detailed analysis of the corrinoid compounds in various animal-source foods using LC/ESI-MS/MS is required.

Heat Degradation Products of B₁₂ from Cooking and Food Processing. Japanese people receive approximately 84% of their daily B₁₂ intake from fish and shellfish.³³ Fish is a good source of minerals, vitamins, high-value proteins, and unsaturated lipids containing eicosapentaenoic acid and docosahexaenoic acid.³⁴ Many studies have suggested that regular fish intake prevents atherosclerosis, thrombosis, and cardiac diseases.^{35,36} Therefore, fish consumption is increasing throughout the world. However, the B₁₂ content of round herring meats decreases by up to approximately 62% by grilling, boiling, frying, steaming, or microwaving.³⁷ Our results indicate that loss of B₁₂ is dependent on the temperature and time of conventional cooking and is further affected by other food ingredients.³⁷ Although there is no loss of B₁₂ during vacuum-packed pouch cooking,³⁷ there is not much detailed data on the nutritional aspects of vacuum-packed pouch cooking; thus, it is difficult to evaluate whether the vitamin preservation is because of the vacuum-packaging or solely because of the lower temperature used.³⁸ Some vitamins (C, B₆, and folic acid) sensitive to oxidation have higher stability in vacuum-packed pouch cooking than in conventional or traditional cooking.³⁹ Retention of B₁₂ in vacuum-packed pouch-cooked meat and fish has been reported to be 100% for veal, lamb, and pork, 87% for beef, 92% for salmon, and 72% for cod.⁴⁰

Microwave ovens are widely used for cooking and food processing and show equal or better retention of various vitamins (B₁, B₂, B₆, C, and folic acid) compared with conventional heating.^{41,42} However, appreciable B₁₂ loss occurs due to degradation of the B₁₂ molecule by microwave heating.⁴³ Microwave heating of hydroxocobalamin, which is predominant in foods, results in the formation of several degradation products.^{43,44} These compounds may result from the elimination of the base portion, a change in the sugar moiety of the lower ligand, and/or skeletal alterations. Thus, the decreased B₁₂ content of various cooked foods appears to be because of the destruction of B₁₂ by heating (Figure 2).

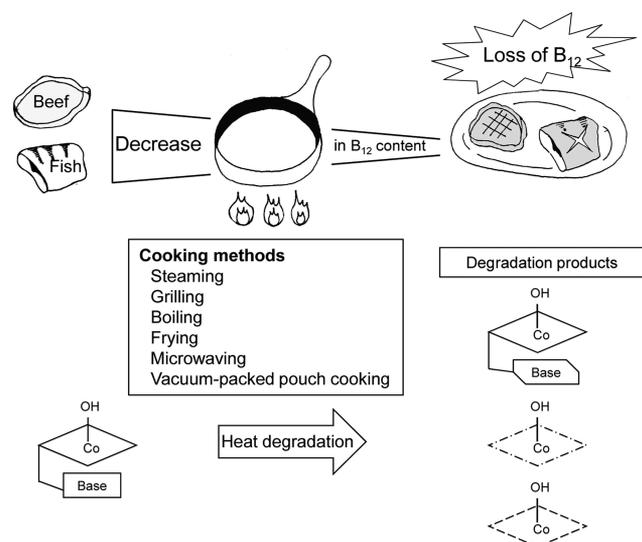


Figure 2. Loss of vitamin B₁₂ during cooking and its heat degradation products.

B₁₂ Degradation and/or Transformation Products by Chemical Treatment and Light Exposure. *Radical Reactions.* Milk is the most important source of vitamins B₂ (B₂) and B₁₂ in the human diet. Photodegradation of B₂ and color change during storage of milk in light have been studied extensively.^{45–47} On exposure to light, B₂ produces free radicals (superoxide anion radical and singlet oxygen) that accelerate the oxidation of tryptophan and other amino acids. Amino acid oxidation is involved in the color change in milk.⁴⁸ To evaluate the loss of B₁₂ in milk during light-induced B₂ degradation, various milk samples were exposed to fluorescent light for 24 h at 4 °C.⁴⁹ The B₁₂ concentration decreased by 1–27%, depending on the type of milk tested. These results indicate that storage in light for a long period can induce degradation of both B₂ and B₁₂ in various types of liquid milk. Light irradiation of B₁₂ in an oxygen-saturated solution indicates that the corrin macrocycle of B₁₂ is degraded by singlet oxygen.⁵⁰ These observations suggest that B₁₂ in milk is significantly degraded by free radicals formed during light-induced B₂ degradation.

An appreciable loss of B₁₂ also occurs in B₁₂-containing multivitamin/mineral supplements⁵¹ because of degradation by addition of a substantial amount of vitamin C (VC) in the presence of copper.⁵² VC or metal ion alone does not degrade B₁₂. However, the combination of VC and copper ion significantly destroyed B₁₂ with formation of large amounts of B₁₂ degradation products, as indicated by ladder-like red spots on silica gel thin-layer chromatography.⁵² Some of these B₁₂ degradation products have been reported to block B₁₂ metabolism in mammalian cells.⁵¹ Degradation of B₁₂ was reduced significantly by the addition of certain antioxidants such as carnosine or anserine,⁵² presumably because of free radicals generated by VC in the presence of copper.

Organochlorides and Other Chemicals. Chloramine-T (*N*-chloro-*p*-toluenesulfonamide) is an active chlorine compound with strong oxidative activity and is widely used as a biocide.⁵³ For a long time, chloramine-T was believed to be nontoxic. It is used in the food industry as a disinfectant for plant sterilization.⁵⁴ It is nowadays used in cosmetics but not foodstuffs. Chloramine-T at 200 ppm for 5–20 min is effective against three virulent Gram-positive bacteria without causing human fibroblast damage in vitro.⁵⁵ Bonnet et al. found that at pH 4.0, 1 mol of chloramine-T, which is a source of electrophilic chlorine (equivalent to Cl⁺),

produces a lactone form (1 mol) of B₁₂, B₁₂[*c*-lactone].⁵⁶ Our unpublished results indicate that certain foods (shiitake mushrooms) contain considerable amounts of B₁₂[*c*-lactone]. Although potential harmful effects of B₁₂[*c*-lactone] on mammalian cells have not been investigated, it may block mammalian B₁₂ metabolism because the similar compound, B₁₂[*c*-lactam], is a well-known B₁₂ antagonist.⁵⁷

Formation of a blue corrinoid from partial degradation of B₁₂ in aqueous bicarbonate has been reported recently.⁵⁸ The corrin macrocycle of B₁₂ is degraded (B-ring-opening), with the formation of 7,8-*seco*-B₁₂.

■ PREVENTION OF B₁₂ DEFICIENCY IN VEGETARIANS

Strict vegetarians are at higher risk for developing B₁₂ deficiency because of low intake of animal-source foods.¹⁰ Thus, it is necessary to identify plant-source foods containing high B₁₂ to prevent vegetarians from developing B₁₂ deficiency.

Fermented Beans and Vegetables. The B₁₂ content of soybeans is low or undetectable; however, tempe, a soybean-fermented food, contains a large amount of B₁₂ (0.7–8 μg/100 g).⁵⁹ Contamination by certain bacteria during tempe production may contribute to its increased B₁₂ content.⁶⁰ Natto, another soybean-fermented food,⁶¹ and Korean soybean products (doenjang, chungkookjang, and kochujang)⁶² contain minute amounts of B₁₂ (0.1–1.9 μg/100 g). Fermented Korean vegetables (kimuchi) contain traces (<0.1 μg/100 g) of B₁₂.^{62,63} Various fermented tea leaves contain very small amounts of B₁₂ (0.1–0.5 μg/100 g dry weight).^{64,65} The juice of fenugreek (*Trigonella foenum graecum*) leaves can be enriched with B₁₂ (12.5 μg/100 mL) by certain lactic fermentations.⁶⁶ The addition of *Propionibacteria* to cabbage during sauerkraut production results in higher concentrations of B₁₂ (7.2 μg/100 g).⁶⁷

Edible Algae. Various types of edible algae are consumed by humans worldwide. Dried green (*Enteromorpha* sp.) and purple (*Porphyra* sp.) lavers (nori) are the most widely consumed edible algae and contain substantial amounts of B₁₂ (approximately 133 μg/100 g dry weight).^{68,69} However, edible algae other than these two species contain no B₁₂ or only trace amounts.⁶ Because the biological activity of algal B₁₂ in humans is unclear, we characterized corrinoid compounds to determine whether dried purple and green lavers and eukaryotic microalgae (*Chlorella* sp. and *Pleurochrysis carterae*) used in human food supplements contain B₁₂ or inactive corrinoids.^{70,71}

To measure the biological activity of B₁₂ in lyophilized purple laver (*Porphyra yezoensis*), the effects of laver feeding were investigated in B₁₂-deficient rats.⁷² Within 20 days of initiating a diet supplemented with dried purple laver (10 μg of B₁₂/kg diet), urinary methylmalonic acid excretion became undetectable, and hepatic B₁₂ (especially coenzyme B₁₂) levels increased significantly. These results indicate that B₁₂ from the purple laver is bioavailable in rats.

Nutritional analysis of six vegan children who had been on vegan diets including brown rice and nori (dried laver) for 4–10 years suggests that consumption of nori (dried laver) may prevent B₁₂ deficiency in vegans.⁷³

Edible Mushrooms. Wild mushrooms are increasing in dietary importance because of their nutritional and medicinal characteristics.^{74,75} Many species of wild mushrooms are widely consumed. Six wild edible mushroom species are popular among vegetarians in European countries. Zero or trace levels (0.01–0.09 μg/100 g dry weight) of B₁₂ were measured in porcini mushrooms (*Boletus* sp.), parasol mushrooms (*Macrolepiota procera*), oyster mushrooms (*Pleurotus ostreatus*), and

black morels (*Morchella conica*). In contrast, black trumpet (*Craterellus cornucopioides*) and golden chanterelle (*Cantharellus cibarius*) mushrooms contain considerable levels of B₁₂ (1.09–2.65 µg/100 g dry weight).⁷⁶ To determine whether *C. cornucopioides* or *C. cibarius* contains B₁₂ or other corrinoid compounds that are inactive in humans, we purified a corrinoid compound using an immunoaffinity column and identified it as B₁₂ by LC/ESI-MS/MS.

Consumption of approximately 100 g of dried black trumpet (approximately 1 kg of fresh mushroom with 90% moisture content) could provide the RDA for adults (2.4 µg/day), although ingestion of such large amounts would not be feasible. Nevertheless, moderate mushroom intake may slightly contribute to prevention of severe B₁₂ deficiency in vegetarians.

B₁₂-Enriched Vegetables. Many studies have measured the B₁₂ content of various vegetables. Only trace amounts of B₁₂ (<0.1 µg/100 g of wet weight of an edible portion) are found in broccoli, asparagus, Japanese butterbur, mung bean sprouts, tossa jute, and water shield.⁷⁷ Mozafar demonstrated that addition of an organic fertilizer such as cow manure significantly increases the B₁₂ content of spinach leaves (17.8 ng/g dry weight).⁷⁸ As sheep fed a cobalt-deficient diet rapidly develop B₁₂ deficiency,^{79,80} microbiological synthesis of B₁₂ in the lumen or intestinal tract is an important B₁₂ source in herbivorous animals. However, our recent⁸¹ and unpublished results indicate that most organic fertilizers, particularly those prepared from animal manures, contain considerable amounts of inactive corrinoid compounds as well as B₁₂.

Hydroponic cultivation is an emerging technology that enables better control of water and nutrient supplies, improves plant productivity, and reduces the use of pesticides.⁸² Attempts have been made to obtain certain B₁₂-enriched vegetables by treatment with solutions containing high levels of B₁₂.^{83,84} Mozafar and Oertli⁸³ reported that uptake of B₁₂ by soybean leaves does not reach saturation even with an extremely high B₁₂ concentration in the nutrient solution (3.2 mmol/L). It has been shown that when soybean seedlings are placed in a solution containing 10 µmol/L of B₁₂ for 24 h, the leaves contain a significantly higher level of B₁₂ (9.8 µg/g fresh weight). Japanese radish sprouts (kaiware daikon) also show significant increases in B₁₂ content (1.28 µg/g fresh weight) after the seeds had been soaked for 6 h in a solution containing 200 µg/mL of B₁₂.⁸⁴ Recently, we produced B₁₂-enriched lettuce leaves cultivated using hydroponics.⁸⁵ The majority of B₁₂ present in the leaves (86%) was recovered in the free B₁₂ fractions, suggesting that B₁₂-enriched lettuce leaves are an excellent source of free B₁₂. These results suggest that B₁₂-enriched vegetables may be of special benefit for vegetarians.

■ PREVENTION OF B₁₂ DEFICIENCY IN ELDERLY SUBJECTS

A considerable proportion of people with low serum B₁₂ levels who do not have pernicious anemia exhibit food-bound B₁₂ malabsorption.¹⁵ Food-bound B₁₂ malabsorption occurs with certain gastric dysfunctions, especially atrophic gastritis with low stomach acid secretion, which is prevalent in elderly subjects.¹⁵ In this section, “true” B₁₂ defines B₁₂ compounds that are biologically active in mammals including humans, but not inactive corrinoid compounds such pseudo-B₁₂. Furthermore, “free” B₁₂ means the protein-unbound B₁₂.

Free B₁₂-Containing or -Fortified Foods. Several investigators have evaluated the efficacy of oral B₁₂ therapy for the treatment of B₁₂ malabsorption in elderly people with B₁₂

deficiencies.^{86,87} Ready-to-eat cereals fortified with B₁₂ constitute a large proportion of the dietary B₁₂ intake in the United States.¹⁷ It has been reported that breakfast cereals fortified with folic acid, B₁₂, and B₆ increase blood concentrations of these vitamins and decrease plasma total homocysteine concentrations in elderly populations.⁸⁸ The effects of B₁₂ supplementation with a milk product on B₁₂-deficient elderly people have also been studied.⁸⁹ Thus, fortified foods have become a particularly valuable source of B₁₂ for elderly people.

Bonito and Clam Soup Stocks and Extracts. The natural food chain would suggest that the meat of larger fish (e.g., tuna and bonito) contains high amounts of B₁₂. Tuna and bonito are popular food items in various countries, and our previous studies^{90,91} have demonstrated that muscles of these fish contain substantial amounts of true B₁₂. In Asian countries, especially Japan, various types of fish soup stocks (primarily dried bonito or small dried sardines) and extracts are manufactured for use as seasoning or flavoring. If the fish extracts and soup stocks contain substantial amounts of free B₁₂, they would be excellent natural sources of free B₁₂ for elderly people with food-bound B₁₂ malabsorption. Although the B₁₂ content of powdered- and granule-type soup stocks is very low (approximately 0.8 µg/L), some liquid-type soup stocks contain considerable amounts of B₁₂ (>5.0 µg/L).⁹² Among the fish extracts tested, the B₁₂ content of the extract made of raw bonito muscle was the highest (40.9 ± 5.5 µg/100 g).⁹² Selected fish extracts (bonito, salmon, and tuna) contained considerably high amounts of true free B₁₂.⁹²

Various types of shellfish extracts are also manufactured for use as seasonings and flavorings. The B₁₂ contents of scallop and freshwater clam extracts were zero or very low (0.1 µg/100 g), respectively, whereas short-necked clam extract contained substantial amounts of true B₁₂ (131.8 µg/100 g).⁹³ Most of the B₁₂ in the clam extract was free B₁₂. These results indicate that the fish or shellfish extracts are natural sources of free B₁₂ for elderly people with food-bound B₁₂ malabsorption.

Fresh clams and their processed food products (e.g., canned clams) are popular food items in various countries. Canned clams are the most readily accessible clam products. The broth of canned clams (boiled plain) contains considerable amounts of free B₁₂ (approximately 2.7–14.1 µg/100 g or 1.3–6.7 µg/can),⁹⁴ suggesting that it is also an excellent natural source of free B₁₂ for elderly people with food-bound B₁₂ malabsorption.

■ CONCLUDING REMARKS

When corrinoids were purified and characterized from various foods, some foods were unexpectedly found to contain inactive corrinoids as well as B₁₂. Because intestinal bacteria synthesize various corrinoid compounds with different bases in the lower ligand, animal manures and human feces⁹⁵ contain substantial amounts of inactive corrinoid compounds (Figure 1). Certain bacteria (as biofertilizers), fish viscera, fish meal, and animal manures are generally used as organic fertilizers for vegetables and grain. Furthermore, B₁₂ is partially converted to a biologically inactive B₁₂ analogue by the reactions of certain chemical reagents such as the biocide chloramine-T. Intact B₁₂, naturally occurring inactive corrinoids, and chemically modified inactive B₁₂ compounds exist in the natural environment. Thus, B₁₂ and other related compounds are concentrated primarily in predators higher on the natural food chain. Foods derived from animal products are the major dietary sources of B₁₂, although B₁₂ is significantly degraded during the cooking and storage of foods (Figure 2). Thus, humans have evolved an IF-mediated gastrointestinal absorption system to select biologically active B₁₂ from

among the various corrinoid compounds and/or B₁₂ degradation products. In addition, the intestinal bacteria of mammals, including humans, synthesize substantial amounts of various inactive corrinoids as well as B₁₂. As shown in Figure 3, these

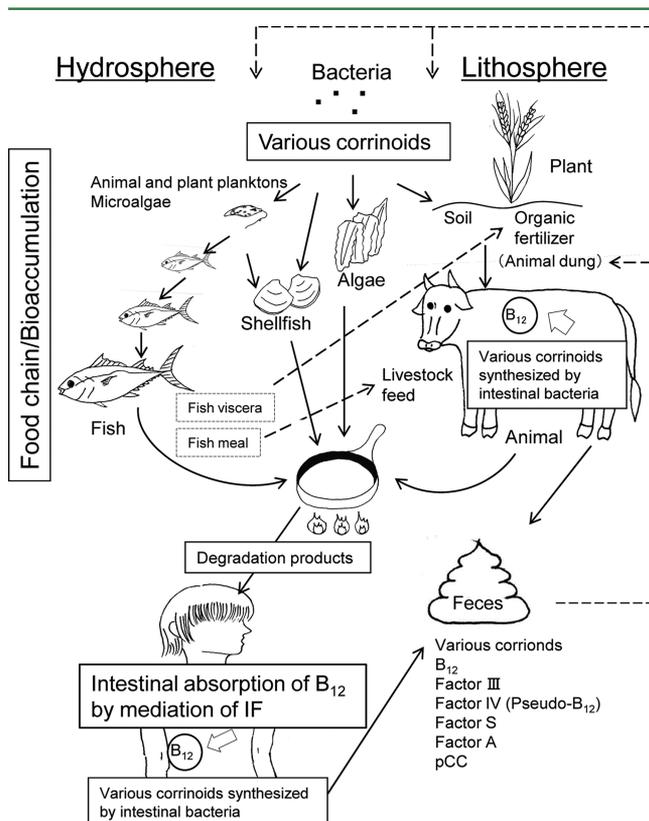


Figure 3. Circulation of corrinoid compounds in the natural environment.

corrinoids are rapidly returned to the soil or water and recirculate in the natural environment.

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Author Contributions

All authors equally contributed to the preparation of the manuscript and have approved the final version.

Notes

The authors declare no competing financial interest.

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