Chapter 86
Laminaria japonica Aresch. and *Ecklonia Kurome* Okam. 昆布 (Kunbu, Kelp)

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86.1 Botanical Identity

Laminaria, *Ecklonia* and some large brown algae of Phaeophyeae are sharing common names "Kelp" and "Kunbu", which are abundant in North Atlantic and Pacific area. To avoid confusion, in this chapter, kelp only represents *Laminaria japonica* Aresch. (Haidai) and *Ecklonia kurome* Okamura (Kunbu). Kelp is not only a popular healthy food, but also an important traditional Chinese medicine (TCM). As a herb, kelp origin, principally includes thallus from *L. japonica* Aresch. of Chordaceae or *E. kurome* Okamura of Alariaceae. *L. japonica* Aresch., was first introduced into China from Japan in late 1920s, and it is now largely distributing along the eastern seaboard of five provinces from the Northern Province of Shandong, Liaoning to southern province Fujian. *L. japonica* is mainly cultured in Rongcheng of Shandong province, *E. kurome* Okamura is mainly distributing in Yushan Island of Zhejiang province and Pingtan of Fujian province of China. Yearly, up to 400,000 tons of fresh kelp, and 35,000 tons of alginate is produced in China making it the largest kelp manufacturer in the world [1].

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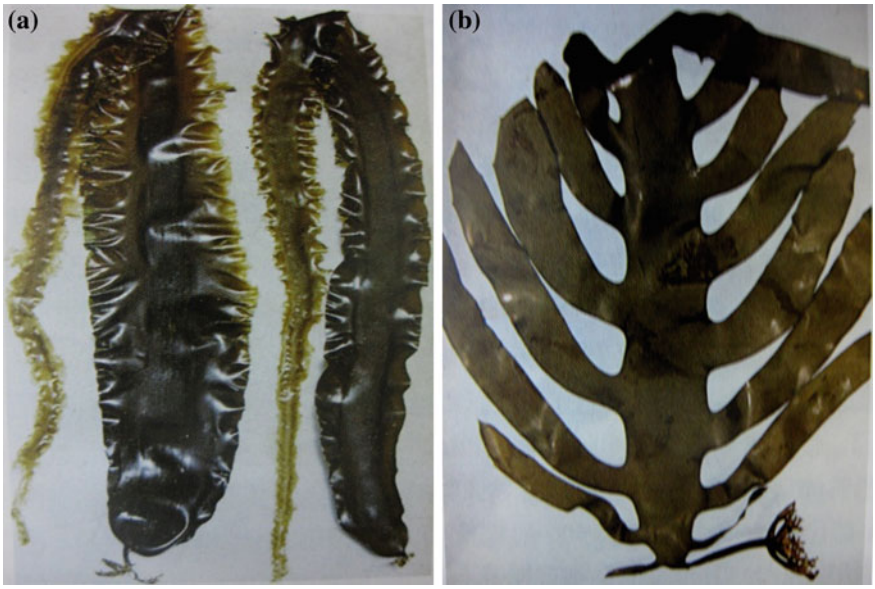


Fig. 86.1 Algae body of *Laminaria japonica* Aresch. (**a**) and *Ecklonia kurome* Okam. (**b**) [1]

L. japonica usually grows on natural rocks 2–3 m deep in shallow sea. Its frond is brown, leathery, single strap-like, flaky, unbranched, 2–5 m high and 20–30 cm wide. The sporophyte of *L. japonica* is complex and leathery. Its parenchymatousthallus is divided into a blade, a stipe and a holdfast. The blade is single stape-like or cleft deeply into palms without ribs, while the stipe is cylindrical or subcylindrical attaching to the substratum by profusely branched rhizoids with many fingers like a haptera. The blade and the stipe roughly have the same structure, consisting of three tissues: epidermis, incrustation and pith. In some species, blades and stipes both have mucus cavity (shown in Fig. 86.1a) [1].

Comparison with *L. japonica*, the algae body of *E. kurome* is smaller, usually 20–100 cm high, and can also be divided into distinct holdfast, stems and blade. Its blade is 3–5 cm in diameter and 4–12 cm long, and has thicker center, pinnate or compound pinnate lobes generally with coarsely toothed edges (shown in Fig. 86.1b) [1].

86.2 Chemical Constituents

Kelp is eaten as Kombu (昆布) in Japan and Haidai (海带) in China, respectively, also in some South and East America countries as sea vegetables or traditional herbs, because they have been known to be rich in nutrients, including

carbohydrates, proteins, fatty acids, vitamins, minerals, dietary fiber, and other bioactive components, such as phlorotannins. For example, *L. japonica* was found to contain 17.1–32.0 % alginic acid, 19.4–45.3 % ash, 0.1–0.7 % iodine [2], 7.50 % crude protein, 1.0 % lipids and 36.0 % dietary fiber [3].

86.2.1 Carbohydrates

Like other brown algae, the cell walls of kelp generally contains carbohydrates including three bioactive components: alginate (**1**), a water soluble polymer composed of guluronic acid (G) and mannuronic acid (M) and their Na^+, K^+, Mg^{2+}, and Ca^{2+} salts, which provides structural support for the algae; Fucose-containing polysaccharides mainly composed of fucose with small of galactose, glucuronic acid and mannose etc. which is usually named as fucoidan (**2**); and laminarin (**3**), a linear or β-1,6-branched β-1,3-glucan (shown in Fig. 86.2) [4].

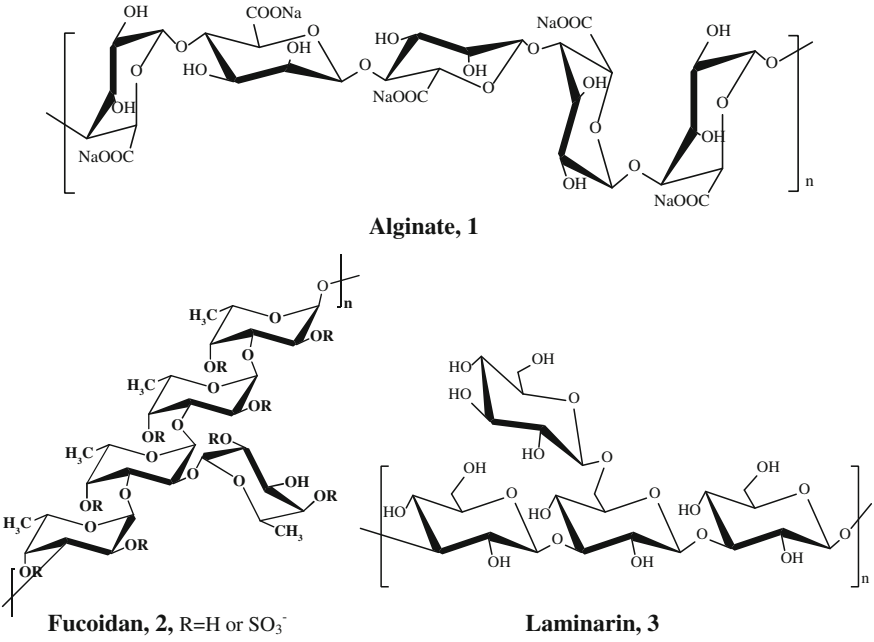


Fig. 86.2 The structures of three polysaccharides from kelp [5]

86.2.2 Fatty Acids

Kelp primarily contains monounsaturated fatty acids and polyunsaturated fatty acids. As reported by Dawczynski et al. [3], the contents and compositions of fatty acids determined in eight kinds of *L. japonica* from China were 36.0 % of palmitic acid (16:1), 12.8 % of oleic acid (18:1) and 16.2 % of eicosenoic acids (20:5). They also found that *E. kurome* contains 0.13 % of daturic acid (17:1), 0.12 % of oleic acid (18:1), 0.094 % of pentadecoic acid (15:1), 0.061 % of eicosenoic acids (20:5) and others of the dry weight algae body [1].

86.2.3 Vitamins

Kelp contains most types of vitamins except vitamin D and K. Nevertheless, vitamin A, C and E are very abundant in *L. japonica* [6].

86.2.4 Mineral Elements

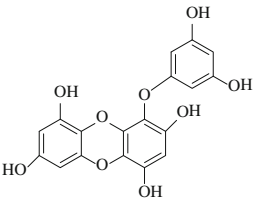
Most of kelps are rich in salts; accounting to 16–36 % of dry weight, including the mineral macronutrients potassium, sodium, calcium, magnesium, chlorine, sulfur and phosphorus, and the micronutrients iodine, iron, zinc, copper, selenium, molybdenum, fluoride, manganese, boron, nickel and cobalt [1, 2].

86.2.5 Phlorotannins

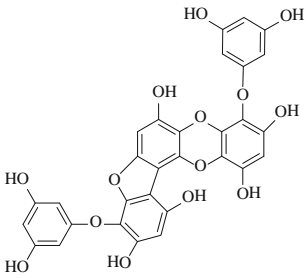
Phlorotannins are a class of bioactive components from *E. kurome* Okamura, which contains m-trihydroxybenzen, eckol (**4**), phlorofucofuroeckol A (**5**), 8,8′-bieckol (**6**), dieckol (**7**), phloroglucinol tetramer and 6,6′-bieckol (**8**) [1]. Recently, Yotsu-Yamashita M and his partner isolated and determined two novel phlorotannins 974-A (**9**) and 974-B (**10**) from *E. kurome* with radical scavenging activities (shown in Fig. 86.3) [7].

86.2.6 Other Constituents

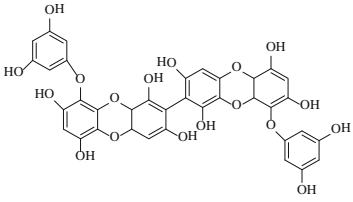
Iodine is the largest proportion of micronutritions in kelp, especially in cultivated fresh seaweed, which generally yields 3–5 %, and even up to 7–10 % [1, 3]. In addition, fucoxanthin, a characteristic orange colored bioactive carotenoid has been



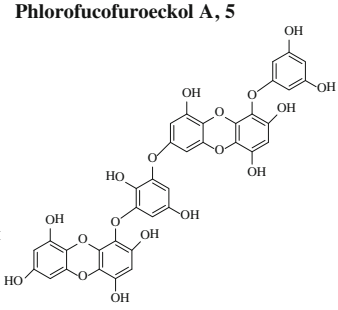
Eckol, 4



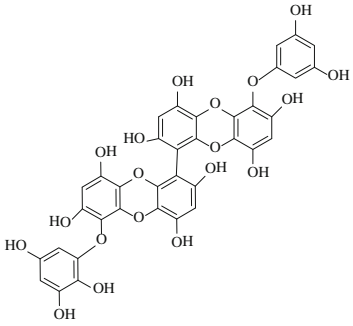
Phlorofucofuroeckol A, 5



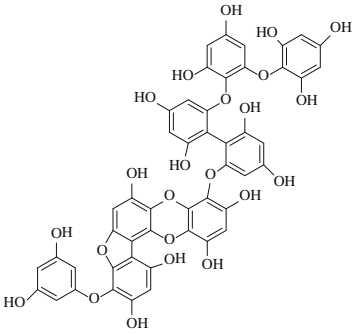
8,8'-Bieckol,6



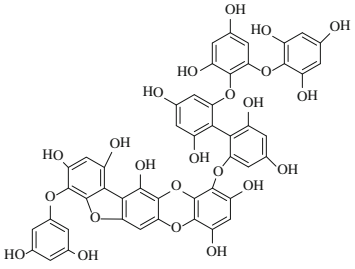
Dieckol, 7



6,6'-Bieckol, 8



974-A, 9



974-B, 10

Fig. 86.3 The structures of phlorotannins from *E. kurome* [1, 7]

extracted from *L. japonica*, *E. kurome* and others edible brown seaweeds [8]. In addition, mannitol, sterols, terpenes, and other small molecule substance are also reported as important components in kelp.

86.3 Pharmacological Studies

Kelp is farmed as commercial seaweed not only for food, but also as the resources for abundant bioactive compounds. For example, kelp is effective to adjust the function of thyroid gland due to the high amount of iodine. Moreover, kelp is abundant in alginate, fucoidan and β-1,3/1,6-glucan, which has anti-coagulant, anti-tumor, anti-virus, anti-oxidant and immunostimulating activities.

86.3.1 Anti-coagulant Activities

Anti-coagulant activity of polysaccharides from kelp is similar with other algal polysaccharides relies on their high content of sulfate groups, which indicates that sulfated kelp polymer is more effective. Interestingly, three low molecular weight fucoidan from *L. japonica* have been exhibited to obviously inhibit coagulant in activated partial thromboplastin time (APTT), thrombin time (TT) and prothrombin time (PT) assays [9]. Zha et al. [10] found that polysaccharides from *L. japonica* showed good potential of enhancing antioxidant enzyme activities in serum of atherosclerosis mice. Moreover, polysaccharides from *E. kurome* were found to have good anti-coagulant activity both in vivo and in vitro; its anti-coagulant activity of each 1 mg is equivalent to 7 U heparin [1]. In the last decade, series of sulfated alginate products, such as PSS and PGMS, have been developed abilities to inhibit aggregation of erythrocytes and blood platelets, which makes great success in Chinese medicine market [1].

86.3.2 Anti-oxidant Activities

Sulfated polysaccharides extracted from *Laminaria* spp. possess excellent anti-oxidant activities, which vary among their molecular weight and degree of sulfation [11]. Wang et al. isolated three sulfated polysaccharide fractions, two galactans and one fucoidan, from *L. japonica* and had their anti-oxidant activities investigated on various in vitro systems, including superoxide and hydroxyl radical scavenging activity, chelating ability, and reducing power. The correlation between the sulfate content and scavenging superoxide radical ability was found to be positive and can be used as an effective indicator to anti-oxidant activity [12]. In addition to this,

Yotsu-Yamashita et al. [7] found that phlorotannins from *E. kurome* also have good anti-oxidant activity in DPPH and intracellular reactive oxygen species assay.

86.3.3 Anti-tumor Activities

Laminarin (β-1,3/1,6-glucan) and fucoidan (sulfated fucan) can affect tumor cells directly or indirectly. Laminarin has the ability to kill tumor cells directly, besides it inhibits the growth of neovascular (new blood vessels). Previous studies have shown that sulfated polysaccharides isolated from *Laminaria* spp. and their hydrolyzed products can be used as apoptosis-inducing agents and anti-cancer drugs, because they inhibit more than 50 % Heps tumor cells but not affect the growth of normal cells [13]. Two fucoidans extracted from the holdfast of cultivated *L. japonica* by Ozawa et al. [14] were proved to have anti-tumor activity against Adenocarcinoma 755-transplanted mice by i.p. and p.o. administration. Moreover, polysaccharides from *E. kurome* also showed good anti-tumor activity for hepatoma cells HepG2 and gastric carcinoma cells SGC-7901; their 50 % inhibiting concentration (IC_{50}) are 592.2 and 649.8 μg/mL, respectively [15]. In the study done by Zhang and his colleagues, fucoxanthin from dietary *L. japonica* has been determined its anti-growth and apoptosis-induction activities against EJ-1 human bladder cancer. Their results indicated that fucoxanthin may act as a chemopreventive and/or chemotherapeutic carotenoid in bladder cancer cells by modulating cell viability [16]. Furthermore, many other extractions of kelp also have showed antitumor activity through the different mode of action in vivo and in vitro.

86.3.4 Anti-virus Activities

A large number of sulfated polysaccharides from brown seaweeds and other polyanionic substances can inhibit various virus infections in vitro containing important human pathogens, such as the human immunodeficiency virus, herpes simplex virus, human cytomegalovirus, dengue virus and respiratory syncytial virus [17]. Fucoidan extracted from *L. japonica* has been studied on anti-virus ability on poliovirus III, adenovirus III, ECHO6 virus, Coxsackie B3 virus, and Coxsackie A16. Furthermore, a sulfated polymannuroguluronate with an average molecular weight of 8.0 kDa, also isolated from this species, has been reported to be in Phase II clinical trials in China against acquired immunodeficiency syndrome (AIDS) [18, 19].

86.3.5 Anti-inflammatory and Immune-Stimulant Activities

Fucoidans isolated from *Laminaria* spp. have been reported to possess immune modulate activities including anti-inflammatory as they regulate and enhance immune function in many ways [20]. As reported by Mizuno, fucoidan was found to exhibit suppressive effects on interleukin-8 mRNA expression in $Caco_2$ through tumor necrosis factor-alpha (TNF-α) production from RAW264.7 cells stimulated with lipopolysaccharide [21]. Also, laminarin has been reported to modulate the immune response as well [6].

86.3.6 Other Activities

Many reports stated other bioactivities of polysaccharides from *Laminaria* spp. and *E. kurome* such as hypolipidemic and hypoglycemic activities, radiation protection, anti-diabetic and anti-fatigue activities. Additionally, an interesting research showed that laminarin has an effect on the preservation of plants [22]. Collectively, kelp has been studied widely for its potential pharmaceutical advantages.

86.4 TCM Applications and Dietary Usage

86.4.1 TCM Applications

As a traditional Chinese medicine, kelp has been used in disease treatment for decades, such as prevent dysphagia, cough, vaginal discharge, emission, wet beriberi, malignant sore, goiter, swollen neck lymph nodes, liver and spleen enlargement and ascites, leaching disease, chronic bronchitis, testicular pain, arteriosclerosis, senile cataract, etc. [1]. The dried raw materials of Kelp and its extracts have been widely applied in clinic in China.

1. Propylene glycol alginate sulfate sodium salt (PSS) is a highly valued heparinoid drug, which is prepared from kelp following hydrolysis, esterification and sulfation [23]. PSS has been principally used for the prevention and treatment of ischemic cerebrovascular disease such as cerebral thrombosis, cerebral embolism and transient cerebral transient ischemic attack, besides cardiovascular diseases such as hypertension, hyperlipidemia, coronary heart disease, and angina pectoris. In addition, PSS has been described to treat disseminated intravascular coagulation, chronic glomerulonephritis and hemorrhagic fever [1].
2. Sulfated propylene glycol ester of mannuronate (PMS) is another heparinoid marine drug, which is developed from kelp alginate following hydrolysis, fractionation, esterification and sulfation. PMS has been used to treat

hyperlipidemia by reducing blood cholesterol and triglycerides levels and increasing plasma high density lipoprotein level [24].
3. Mannitol, which is mainly extracted from kelp for decades in China, can be used clinically to treat cerebral edema and glaucoma, extensive burn, burn caused edema, renal failure, and ascites [25].
4. Iodine prepared from kelp can be used in iodine-glycerol production, which is a mixture of potassium iodide-iodine, water and glycerol. In dental clinic, iodine-glycerol is a common agent for oral mucosal ulcers, gingivitis and pericoronitis treatment [25].
5. Haikunshenxi capsule is the mainly composed of fucoidan, which is separated from kelp. It has a great benefit in curing chronic renal failure in China [24].

86.4.2 Dietary Usages

Most people in Asian and western countries share different diet habit. A preference for seaweeds, particularly brown seaweeds (kelp), seems to be confined to the Asian population. As mentioned above, kelp is known as the "longevity food" and it is rich in polysaccharides, trace elements, vitamins and other nutrient substances. Thus, it becomes a great valuable traditional Chinese healthy food that is suitable for the elderly people, especially. Several studies have shown that kelp has possessed remarkable properties making them a wonderful component of dietary supplements. Besides family cooking as salad, soup, fries and other process, a variety of new types of food made with kelp has been developed, such as fermented kelp beverage, kelp health tea, kelp chili sauce, kelp sausage and kelp fiber noodles. Some examples are listing here as follows:

1. Kelp beverage: Xu et al. [26] developed a compound beverage of *E. Kurom* with *E. Kurom* juice and lotus leaf juice in the proportion of 2:3, together with 0.3 % maltodextrin as debitterizing. The fermentation drink of kelp was produced from *L. Japonica* as the raw material by lactic acid fermentation, whose optimal formula is 50 % of natural kelp fermented juice, 0.08 % of citric acid and 2 % of sugar [27].
2. Kelp health tea: Gu et al. [28] has described the processing technology and operation key points of a low-cost but multi-functional natural health drink made from black rice, kelp, and green tea. Citric acid and water solution (2 %) has been applied to remove the fishy flavor of kelp. According to the national food safety standards, kelp has been soaked and washed with water 12–24 h to get rid of extra arsenic salt before further processing. Besides the nutritional values of this seaweed, the addition of kelp extract can be part of stabilizers and thickeners for drink production.
3. Kelp frozen yogurt: Kelp and skim milk powder have been used as raw materials in Fu's study for fermented seaweed and black sesame frozen yogurt [29]. The ratio of kelp to water, the addition amount of sugar and skim milk powder

were taken as 3 factors, respectively, when designed the experiments. The results suggested that when the ratio of kelp to water was 1:20, with 6 % of sucrose, 13 % of skim milk powder and 5 % of inoculating lactic acid bacteria, after fermentation at 42 °C for 24 h, with addition of agar, sugar and black sesame, the final yogurt jelly had unique milky-white color, homogeneous tender, moderate sweetness and rich nutrients.

4. Kelp sausage: A new kind of vegetable-rich sausage product has been developed by Dong's group, which consists of carrot, kelp and pork [30]. This sausage contains great portion of protein, dietary fiber, mineral matter and multi-vitamins, as well as it meets the requirements of modern diet and has a great market value.
5. Kelp chili sauce: Yuan et al. has introduced the preparation of kelp chili sauce with 30 % chili, 10 % salt, 6 % garlic, 5 % kelp, 2 % sugar, 1 % modified starch and 0.7 % xanthan gum to make it delicious and nutritious, besides stimulating appetite and helping in digestion and absorption [31].

86.5 Clinical Evidences

Due to kelp's amazing medical benefits, it has been used as a traditional Chinese medicine since centuries, and it has been listed in the Pharmacopoeia of the People's Republic of China. In addition to PSS, PMS and FPS as mentioned above, kelp has also been used widely in the clinical applications.

86.5.1 Treatment of Infusion Phlebitis

Phlebitis is a common adverse reaction during infusion. Due to relieving swelling and pain effects of kelp, Wang has developed a new treatment using kelp combined with specific electromagnetic irradiation (TDP), and compared with the traditional magnesium sulfate therapy on 184 cases of infusion phlebitis patients which were divided randomly into observation group and control group, respectively [32]. After irradiated under specific electromagnetic wavelength for 20–30 min, the phlebitis area was covered by fresh or rehydrate kelp in observation group. Other than the poor effect of magnesium sulfate control, TDP irradiation increased the absorption efficacy of the mannitol, alginate, iodine and other trace elements from the kelp which reduced the treatment period and satisfied the patients.

86.5.2 Treatment of Ophthalmic Diseases

Kelp eye drops containing vitamin B and C have been reported to treat commotio retinae, vitreous opacities and senile cataract significantly [1]. Studies have shown that the kelp-based iodine could inhibit connective tissue proliferation, enhance inflammatory exudation absorption and accelerate blood circulation. This slowly absorbed and excreted iodine is believed to work more effectively the longer it remains in body than other iodine products.

86.5.3 Other Clinical Applications

Kelp has also been concerned by scholars for its wide original and notable benefits for many other treatments in clinic. Reviews have packed up the documents about the clinical application of kelp, such as thyroid diseases, hypertension, mammary gland hyperplasia, chronic pelvic inflammatory disease, cancer, icteric viral hepatitis, astriction, etc. [33].

86.6 Safety Evaluation and Toxicity Data

As a traditional Chinese vegetable, especially more common in coastal areas, wild and cultured kelp and their extracts have been proved notoxicity and no mutagenic effects in the mice experiments [34]. In intragastric administration doses of 21,500, 10,000, 4640 and 2150 mg/kg, no animal death was observed for five days. Cumulative toxicity test showed no toxic accumulation of *Laminaria* extracts in animals observed within 20 days. Further Ames experiments showed that it did not induce gene mutation to four histidine-deficient *Salmonella typhimurium* strains, which suggested it as a safe food additive and medicinal material. In an experiment where female mice fed normal diet to 2.4 g/kg · day dose and given kelp capsules intragastrically for 18 days, the experimental group showed no significant difference compared with the control group in the indicators of pregnancy rate, implantation rate, embryonic development, fetal body weight, body length, tail length, and bone development [1].

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