USES OF ALGAE IN THE CONTEXT OF PROBLEMS OF THE ENVIRONMENT AND OF PUBLIC HEALTH

*Milena Bruno,
**Elvira Gentile,
*Giuseppe Salvatore

6th part

ALGAE-BASED PHARMACEUTICAL PRODUCTS

Algae as a source of pharmaceutical substances have already been considered in Part Five of this series of articles (Bruno et al., 2004) regarding the preparation and uses of the hydrocolloids that can be obtained mainly from brown algae (Pheophyceae: Laminariaceae) and red algae (Rodophyceae: Gigartinaceae and Gelidiaceae):

- Laminariaceae (*Laminaria spp., Aschophyllum nodosum, Macrocystis pyrifera*) for alginic acid and alginates, used as an anti-acid and in problems of gastro-esophageal reflux;
- Gigartinaceae (*Chondrus spp.; Gicartina spp.*) for the carrageenans that come under the category of mechanical laxatives (bulk-forming laxatives);
- Gelidiaceae (*Gelidum spp.*) for the agar agar which is also used as a mechanical laxative, encouraging peristalsis and intestinal evacuation and increasing the water content and volume of the faeces.

The presence of these phycocolloids in medicinal products has also already been mentioned in the previous article (Bruno et al., 2004).

Here, we wish to report on the pharmaceutical uses of algae-based products (powders and extracts) mentioning:

- medicinal products, including OTC products;
- homeopathic products;
- magistral and officinal preparations made up in the chemist's.

In the Fourth Edition of the European Pharmacopoeia and supplements up to 4.8 (2002 – 2004), the texts of which, in English and French, came into force in Italy as part of the Official Pharmacopoeia of the Italian Republic 11th Edition, 2002), there is only one monograph devoted to algae under the name of Kelp; this was introduced with Supplement 4.6 and replaces and amends the previous entry entitled Fucus.

Kelp (Fucus vel Ascophyllum; Eur. Ph. 4th Ed., Suppl. 4.6, 01/2004:1426)

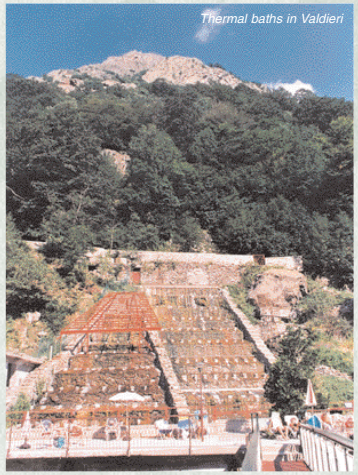
The drug is made up of the desiccated and fragmented thallus of *Fucus vesiculosus L. or Fucus serratus L. or Ascophyllum nodosum* Le Jolis. It contains not less than 0.03 % and not more than 0.2 % of total iodine, calculated with reference to the desiccated drug. The label on the packaging must specify the name of the species of Kelp present.

It has a salty, mucilaginous flavour and an unpleasant odour, typical of sea algae. The monograph, as well as the above definition and features, contains three identification tests. One is the differentiated macroscopic botanical description of the three aforementioned species. The thallus is presented in fragments of coriaceous consistency, from dark brown to greenish brown in colour, sometimes covered with a whitish bloom; it consists of a linear lamina with a dichotomous ramification with prominent median pseudonervations. *Fucus vesiculosus* typically shows fronds with rounded edges and single or paired air bubbles (aerocysts). The extremity of some ramifications are ovoidal in shape and slightly broadened and show numerous reproductive structures called conceptacles. In comparison, *Fucus serratus* has fronds with serrated edges without aerocysts and the conceptacles are less swollen. The thallus of *Ascophyllum nodosum* has irregular ramifications and does not have the median pseudonervation; it shows single air bubbles that make the edges of the thallus more protruding, therefore it appears gnarled. The falciform conceptacles are at the ends of small ramifications. The thallus, when reduced to a powder (355) appears blue-greenish to grey-brown in colour and is used for the other two identification tests: the microscope test (with the observation of numerous fragments of the cortical area with regular isodiametric cells with a brown content and fragments of the medullar area with cylindrical cells, in a row, and with thick, colourless, shining and mucilaginous walls, often with a grey-brown content) and the chemical assay on powder treated with hydrochloric acid at 2% (the residue then has added to it a solution of sodium carbonate of 200 g/litre and is centrifuged; in the supernatant, brought to pH 1.5 with sulphuric acid, a flocculent white precipitation is observed).

The drug must meet the following nine assays:

- extraneous substances: maximum 2 % m/m;
- arsenic: maximum 90 ppm;
- cadmium: maximum 4 ppm;
- lead: maximum 5 ppm;
- mercury: maximum 0.1 ppm;
- swelling rate: minimum 6;
- loss on desiccation: maximum 15 %, determined on 1,000 g in oven at 100 – 105°C;
- total ashes: maximum 24 %;
- insoluble ashes in hydrochloric acid: maximum 3.0 %.

The quantitative determination of total iodine is made by volumetric titling with sodium thiosulphate 0.01 M in the presence of starch water of the final solution obtained treating 1,000 g of pulverised drug so that it releases iodine (1 ml of sodium thiosulphate 0.01 M is equivalent to 0.2115 mg of iodine).


Thermal baths in Valdieri


Prionitis Schmitziana

THE PRODUCTS ON THE MARKET

The interest in these algae, in particular for Fucus vesiculosus, is due to the presence of iodine, an essential element required for the normal activity of the thyroid, as it is a constituent of the thyroid hormones T4 (thyroxine; it contains 65% in weight of iodine) and T3 (tri-iodiothyronine; it contains 59 % in weight of iodine) for the optimum maintenance of the basal metabolism and normal growth and development of the organism. The thyroid contains about 60 - 80 % of the total quantity of iodine in the human body, which is about 10 - 20 mg of iodine in the normal adult (SCF, 1994).

Both situations of deficiency or excess of iodine in the human organism alter the normal function of the thyroid gland and the general state of health. Deficiency states of iodine show themselves with various disorders (Iodine Deficiency Diseases, IDD); maternal deficiency is the cause of infertility, of a greater rate of abortions, perinatal and neonatal mortality, congenital anomalies including neurological cretinism, psychomotory delay and a reduced mental function in children. All this may have a strong impact on the socio-economic development of a population: in some regions of the world, goitre and hypothyroidism may even become endemic. On the other hand, high levels of the consumption of iodine are associated with toxic nodular goitre and hyperthyroidism, where there is an altered functionality of the thyroid in the use of iodine; people with a pre-existing situation of an iodine deficiency are also exposed to this risk. The symptoms of prolonged exposure to non-physiological levels of iodine include irritation of the eyes, serious cutaneous rashes, gastrointestinal disorders, diarrhoea, increased salivation and inflammation of the oral cavity and of the throat.

The ingestion of iodine in a quantity of less than 5 mg/g day/adult is not toxic (SCF, 1994); levels of 1 - 2 mg/day appear to be safe (Freund et al., 1966).

A balanced iodine equilibrium that ensures a normal thyroid function in the adult can already be obtained with levels of consumption of iodine of 40 - 100 µg/day. In conclusion, the SCF (1994) recommended the following values: - average requirement, 100 µg/day; - level of reference for the population, 130 µg/day; - minimum threshold of consumption, 70 µg/day. In other sources, the value of the daily iodine requirement is shown at 150 µg/day (E Commission, 1994).

These levels are normally ensured by a balanced diet and with water to drink. However, there is therapeutic or prophylactic administration of iodine through the use of standardized pharmaceutical products or other products that contain it. An example is given by iodinated salt and/or iodated cooking salt; these salts have potassium iodide and/or iodated potassium added to them in order to guarantee an ionic iodine content of 30 mg/kg of product (Ministerial Decree no. 562 of 10th August 1995) .

Algae and other sea plants are the most plentiful natural source of iodine. The Chinese already had knowledge of this in 3000 BC, when they would cure goitre by feeding the patient with algae;

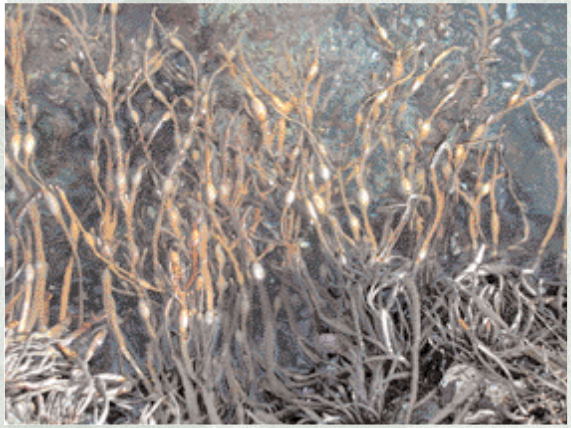
Fucus vesiculosus was the first algae used for this purpose. For this reason, the recommendation of not exceeding in consumption is recommended, as there is evidence of a greater rate of goitre in consumers of algae for whom the ingestion of iodine exceeded 10 mg/day (Suzuki et al., 1965).

In the pharmaceutical sector, amongst the algae mentioned, *Fucus vesiculosus* or Marine Oak is the most widely used algae; this is not only due to the presence of iodine, but also to the content of carbohydrates, of which about 65% is made up of alginic acid. Therefore, preparations based on this algae are traditionally used in the treatment of thyroid diseases, obesity, excess weight, arteriosclerosis and problems of digestion, as well as to purify the blood (OEMF, 1996).

As far as the efficacy of the drug in particular is concerned, administered for the presence of iodine, this has not been demonstrated at doses of iodine below 150 _g/day; on the other hand, at doses of iodine greater than 150 _g/day, there exists the danger of inducing and worsening hyperthyroidism. For these reasons the drug is on the negative list, which includes those drugs with a therapeutic rate which is too narrow or with an activity that has not been sufficiently demonstrated; this does not entail any prohibition of use, but rather prudence and knowledge of the limits of use (E Commission, 1994). Another reason that limits the use of Fucus vesiculosus in iodine therapy is the difficult standardization of the drug due to the fact that its iodine content varies according to the marine habitat of origin (0.03 % and 0.1 %, respectively in algae of the Baltic Sea and the North Sea). No less important is also the fact that the iodine is found in organic form and mainly in inorganic form (as an iodide) with a different bioavailability.

The presence of alginic acid is the other reason for the use of this drug in disorders of the digestion as an anti-reflux and in the treatment of obesity and overweight subjects. In this last respect, *Fucus vesiculosus* has been attributed with a slimming power in cases of obesity and overweight; but the most accredited action is that of stimulating the basal metabolism and the thyroid function. Indeed, the thyroid hormones, thyroxine (T4) and tri-iodiothyronine (T3) are recognised as playing a fundamental role in decoupling the oxidative phosphorylation at mitochondrial level. From this disassociation there derives a decrease of the high energy triphosphate compounds (ATP, GTP, etc.) and therefore an increase in the energy expenditure and a decreased availability of the same compounds for the synthesis of lipids or other macromolecules (Currò and Amadeo, 1976).

OTC products based on Fucus vesiculosus in association with other plant extracts are: (OEMS, 2003): - Fave di Fuca tablets, containing dry extract of Fucus vesiculosus with an


Ascophyllum nodosum


Tipcal moulds on the stairs.
Thermal baths in Valdieri
(G. Bonetto)

alginic acid content of more than 12 % (126 mg), dry extract of Cascara sagrada with a content of anthraglucosides greater than 7 % (170 mg) and dry extract of alder with more than 2.5% (222 mg) of anthraglucosides; - Neoform granulate, containing dry extract of marine oak with an iodine content > 0.2 % (5 g), dry extract of alder with a content of hydroxyanthracenic heterosides of 7.5/9 % (4 g), excipients (fluid extract of rhubarb 6 g, lactose 85 g, mint essence 0.5 g, ethylic alcohol 95 % 0.5 g). Both OTC products come under the same Anatomical Therapeutic Chemical category (contact laxatives in combination; ATC A06AB20).

The complex and unitary homeopathic medicines based on algae (OEMF, 2003) include those shown in the table. The unitary homeopathic medicines are all by the same pharmaceutical company and come in different forms and dilutions. These medicines are mainly based on Fucus vesiculosus and only three unitary homeopathic medicines are based on Laminaria digitata. The last-named drug is also considered in the negative list of the E Commission (1994).

MAGISTRAL AND OFFICINAL PREPARATIONS

Algal preparations (in the form of hydrocolloids, fragments or powder of thallus, fluid, soft and dry extracts, tincture) are the object of magistral preparations in chemists' for the preparation of the formula and delivery of the finished product to patients. The main therapeutic indication is in relation to gastrointestinal disorders and disorders of the metabolism, particularly for slimming or draining purposes. In particular, the therapy of obesity and excess weight takes advantage of preparations that can stimulate diuresis (for example, extracts of birch, maize stigma, cherry stalks, goldenrod, spiraea, dandelion, fumitory and pilosella) and the thyroid function (in particular extracts of Fucus and Laminaria) and choleretic and cholagogue preparations (for example, extracts of artichoke, dandelion, fumitory, rosemary and boldo). In the treatment of obesity, agar is included amongst the "anti-hunger" agents like glucomannan, Psilio cuticola and Guar flour. These agents, on contact with water, swell in the stomach, causing a sense of satiety and then helping intestinal transit, incorporating residual food and decreasing absorption. It is sometimes necessary to associate a treatment with plants having a sedative and calming activity (passion flower and valerian), as for example in cases of psychological troubles with imbalance of the appetite and crises of bulimia.

Amongst the formulas based on algae described in literature that can inspire possible magistral and officinal preparations, those of Mercati and Sgrignani (1998) can be mentioned by way of example and to which reference should in any case be made for the opportune in-depth study; in practical use, however, special attention should be paid to the presence of iodine.

350 mg gelatine capsules

Fucus thallus	30 %
Laminaria thallus	20 %
Spirulina	10 %
Dandelion tops	15 %
Birch leaves	15 %
Fumitory tops	10 %

Mixture of hydroalcoholic extracts with essential oils

Fucus thallus	30 %
Dandelion root	30 %
Birch leaves	20 %
Spirea tops	19 %
Essential oils in equal parts of:	
Juniper and lemon	1 %

Infusion at 3% for 15 minutes of a mixture of plant drugs and Fucus

Fucus thallus	35 %
Matè tops	25 %
Birch leaves	20 %
Star anise fruit	10 %
Peppermint leaves	10 %

Infusion adjuvant in slimming therapies – decoction at 4 %

Marine oak (Fucus) thallus	20 g
Alder bark	15 g
Couch grass rhizome	15 g
Ash leaves	15 g
Mallow flowers and leaves	15 g
Liquorice root	15 g
Sweet orange yellow zests	5 g

Tisane for obese subjects with fluid retention - 4 % infusion

Marine oak (Fucus) thallus	20 g
Ash leaves	15 g
Couch grass rhizome	15 g
Liquorice root	15 g
Mallow flowers and leaves	15 g
Alder bark	10 g
Asparagus root	5 g
Sweet orange zest of fruit	5 g

Tisane for obese subjects with fluid retention - 3 % decoction

Marine oak (Fucus) thallus	40 g
Peppermint leaves	20 g
Alder bark	20 g
Asparagus root	20 g

Slimming syrup

Fluid extract 1:1 of:	
Marine oak (Fucus) at 20 °C	30 g
Alder at 20 °C	10 g
Sweet orange at 25 °C	5 g
Simple syrup or apple concentrate	55 g

Slimming capsules

Nebulised dry extract of:	
Marine oak (Fucus), organic iodine	0.05 % minimum
Alder, hydroxyanthracenic heterosides	7.5 % minimum
Equisetum E:D = 1:4 ana	0.100 g
Inert excipient as required	

In Formulario pratico di Fitoterapia (Murari Colalongo, 1988), from which these preparations have been taken, the recommended doses are shown for:

- *Fucus vesiculosus* L. or desiccated Marine oak thallus: slimming, metabolic stimulant.

Fluid extract	30 drops twice a day (1g = 30 - 35 drops)
Nebulised dry extract	0.300 g/capsule; 2 - 4 capsules a day
Mother tincture	50 drops, 2 - 3 times a day

- *Chondrus crispus* L. or Marine lichen thallus (Carrageenan , Irish Moss or Chondrus crispus): antitussive, emollient, bulk-forming laxative

1% decoction	ad libitum

Formulations based on marine oak, marine lichen, Irish lichen are suggested by Chiereghin (1992):

Slimming tisane (Chierighin)

Fucus vesiculosus

Marine oak t.t.	20 %
Couch grass root t.t.	20 %
Cherry stalks t.t.	20 %
Asparagus root t.t.	20 %
Marine lichen t.t.	10 %
Birch leaves t.t.	10 %
Mallow flowers and leaves t.t.	10 %

ALGAE – SPA ENVIRONMENTS – WELL-BEING

In some spa environments, characterised by particular natural, geophysical, environmental, thermo-mineral and bioclimatic conditions, a particular algal vegetation develops, mixed with a characteristic microbial flora in the flow channels of the spa waters of a sulphuric nature, exposed favourably to the sunlight. Masses of natural materials, long felts or filamentous living carpets, "that proliferate until maturity", taking on a mucous and viscid consistency, are formed close to the surface of the slowly flowing water.

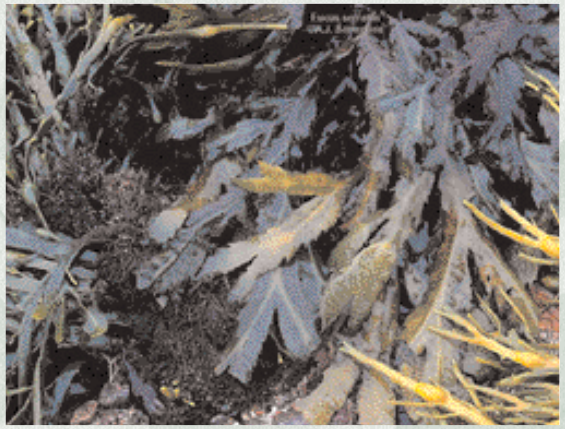
These natural formations historically were and are still described macroscopically as "moulds" (Marchisio, 1898) or "natural organic plant peloids" formed by a solid component (mentioned above) and a fluid component formed by the sulphurous water.

Popular beliefs and experiments, although empirical, but with a more medical character, that have matured in time in those places on the possible and positive therapeutic virtues of the moulds for various troubles, led to the first spa establishments. These were followed by the present-day spas, where the moulds that are used are not those of the natural water channels but come from cultivations on special steps that are built on inclined levels so that the sulphurous water passes over them with a slow and laminar flow.

The masses that are formed are removed from their seats in the form of blocks, of dimensions of about 600 cm2 and 5 cm in thickness, which are called "placentas". These, previously thermalized in sulphurous water at a temperature of 45 – 48 °C, are then applied as packs on the cutaneous areas of the visitors to the spas suffering from certain forms of arthritis, subacute and chronic rheumatism (Ciferri and Pignatti) and from cutaneous psoriasis (Nappi et al., 1966). This technique has been traditionally applied for about three or four centuries and was described by Marchisio in 1898.

The composition of the moulds is complex, including a variety of algal species, bacteria, protozoa, nematoids and larvae of arthropods, especially insects. The algae include blue algae or Cyanophyta, green algae or chlorophyta; the most characteristic species is *Phormdium gelatinosum*; the micro-organisms are those belonging to Beggiatoaceae, in particular Schizomycetes of the Beggiatoa, Thiothryx, Thiploca and Thiospirillopsis genera, i.e. colourless sulphur bacteria living in spa waters that draw their chemosynthetic energy from the oxidation of hydrogen sulphide to sulphur that is accumulated in the cell body. The bacteria also have the function of degrading the organic substance of the dead algae. Naturally, a variety of other factors are influential in this, such as the average temperature and the oxygenation of the sulphurous waters and the light that is different in the strata of algae. In particular, the temperature conditions life: above 50 °C there is a rarefaction of the flora, including microorganisms of the schizomycetic type; between 45 – 50 °C the fundamental mass of blue-green algae develops in particular; algae that are less thermophile but with a faster and more luxuriant growth develop between 35 and 40 °C. The algal felts, deemed more suitable for therapeutic purposes, are those which have reached "maturity", i.e. those which have developed in the shelves of the "mould-house" between 45 and 50 °C and the lower layers of which are no longer exposed to the light, therefore the cells enter in lysis, the cell walls gel so that the "placentas" take on a mucous and viscous consistency to the touch (Ciferri and Pignatti).

In brief, this is the story of the Baths of Vinadio and of the Thermal Baths of Santa Anna di Valdieri, which are both in the province of Cuneo. The first accounts of Valdieri, as "*a place for the health of people and for pleasure*", at 1346 metres above sea level and sheltered by Monte Matto, date back to 1559 in a letter written to Emanuele Filiberto by a subject who complained of the fact that in *Valdieri… there are excellent baths, which due to the ignorance of the inhabitants are not visited very much*". The first establishment to take the waters was built in 1588, and managed first by a "*bath-keeper*" and then by the municipality. After a long period when it was sadly famous for the inadequacy of the structure, despite interventions and the authoritative interest of Carlo Emanuele I (1613), of illustrious physicians of the times, of Carlo Emanuele III, Duke of Savoy and King of Sardinia, for whom a building called the "baraccone" was built in 1755, Carlo Alberto who spent time there in 1833 and Cavour himself who thus spoke in favour of building the new Spa Establishment (1855) " *Valdieri is the richest place in waters for the health that exists in the country and perhaps in the whole of Europe. To tell the truth, I do not know whether there exists another place where such a great variety of very efficacious waters can be found altogether...*". And it was thus that the first stone was laid by Victor Emanuel II; but history continues with other information and other figures.



Fucus serratus

These brief historical notes were taken up by Gian Franco Bianco in an article (Le Terme di Valdieri), to which reference should be made for the other information and historical curiosities on visitors to the spa as regards their habits, social entertainment and their therapeutic expectations, but the effectiveness of the treatment provided, including with the moulds, remains a curiosity that we would like to study in greater depth, also as a tribute to those algae that seem to be protagonists and which we would like to know better in their identity and nature.

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**** Istituto Superiore di Sanità, Roma***
***** Accademia di Storia dell'Arte Sanitaria, Roma***

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