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A Potential Application of Algae as a Complementary/Integrative Therapy in Veterinary Medicine

Masaaki Tamura*, Susumu Ishiguro

Department of Anatomy & Physiology, Kansas State University College of Veterinary Medicine, Manhattan, KS 66506, United States

Review Article

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***For Correspondence:**

Masaaki Tamura,
Department of Anatomy & Physiology, Kansas State University College of Veterinary Medicine, Manhattan, KS 66506, United States

E-mail: mtamura@vet.ksu.edu

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ABSTRACT

Although the nutritional and medicinal properties of algae have been studied for the last several decades, its value in veterinary medicine is widely unknown. Algae are found in fresh water, saltwater and soil, and they are rich in diversity. It has been shown that algae contain various nutrients that are beneficial for human and animal health as well as food/feed industries. Alga's whole bodies, their extract, and bioactive molecules purified from algae have shown medicinal properties that are potentially beneficial for animal health, however, the usage of algae is still in confusions. In this minireview, potential applications of algae in veterinary medicine and its nutritional value for domestic animals are discussed. In addition, the possible existence of novel immune modulative materials in cell wall membrane of Chlorella sorokiniana will be discussed based on our recent discovery.

INTRODUCTION

Over the years, there has been vast research into the use of natural products for medicinal purposes [1]. Algae are some of such naturally occurring resources that show huge promise. Algae is a general term for

photosynthetic eukaryotic organisms that can be found throughout the world. The organisms in this group consist of a wide variety of species; from micrometer sized unicellular microalgae such as Chlorella, to meter sized multicellular macroalgae such as seaweed. Algae have been reported to contain large amounts of various beneficial components, such as proteins, peptides, amino acids, beta-1,3-glucan, vitamins, polyunsaturated fatty acids, polysaccharides etc. [2]. Therefore, the whole cell powder or crushed cell body powder of algae is taken as a nutritional and functional dietary supplement and contributes to human health [2]. It has been shown that a dried powder of microalgae or its extracts in water or polar organic solvents has potential medicinal properties, such as anticancer [3] antimicrobial [4] antiviral [5] antioxidant [6] anti-inflammatory [7] and anti-obesity [8] etc. These medicinal properties of microalgae can potentially develop into novel therapeutics in the field of both human and veterinary medicine. Microalgae and related products are also usable as a potential resources of feed and nutrition for livestock and poultry [9] as well as pets [10-12].

MICROALGAE IN VETERINARY MEDICINE

There are potentially wide applications that can be derived from microalgae, particularly Chlorella in the treatment of diseases such as inflammation, cancer, and infectious disease. The use of microalgae as a nutrient source for pets was evaluated and deemed nutritionally beneficial. Consequently, pet foods containing microalga are commercially available as healthy functional food for dogs and cats. Souza et al. (2019) used green microalgae *Schizochytrium sp.* as a source of docosahexaenoic acid (DHA) and evaluated the aptitude as a dietary component and the effect on immunity in dogs [13]. DHA is one of the polyunsaturated fatty acids (PUFA) which is known to be an essential nutrient for dogs' growth and survival. In addition, DHA is known to improve immune functions in dogs and other species [14, 15]. However, since the conversion of alpha-linolenic acid to DHA is inefficient in dogs [16] the effect of dietary supplementation of DHA was evaluated in this study. Supplementation of 0.4% of *Schizochytium sp*. in the diet as a source of DHA increases the digestibility of nutrients and metabolizable energy. It also increases the number of phagocytic cells and the intensity of phagocytosis in monocytes in the blood. Notably, it does not alter dog's palatability, fecal characteristics, or biochemical blood parameters. As a source of DHA, *Schizochytrium sp.* was also evaluated in cats [17]. In this study, the influence of DHA-rich microalgae diet on the serum level of inflammatory markers including prostaglandin E2 (PGE2), acute-phase proteins (ceruloplasmin, haptoglobin, α-1-acid glycoprotein, albumin and transferrin) and 12-hydroxyeicosatetraenoic acid (12-HETE), before and after neutering was evaluated. The DHA-rich microalgae diet did not affect serum level of 12-HETE, while serum level of PGE2 and albumin were decreased significantly. The number of platelets in blood was observed as an indicator of local inflammation. Feeding of the DHA-rich microalgae diet increased basal level of platelet count. Although platelet count was significantly decreased after neutering in both normal and DHA-rich diet groups, platelet count in the DHA-rich diet group was significantly higher as compared to the normal diet group. In this study, dried *Schizochytrium sp*. containing DHA (n-3 fatty acid) was supplemented by replacing poultry fat (n-6 fatty acid). It is known that n-3 fatty acid has an anti-aggregatory activity, whereas n-6 fatty acid has a pro-aggregatory activity. The result suggests that supplementation of DHA (n-3 fatty acid)-rich *Schizochytium sp*. decreased the ratio of n-6 fatty acid in the diets, therefore anti-aggregatory activity become predominant in the blood of cats served with a DHA-rich microalga diet. These results also suggest

that a DHA-rich microalga diet regulates the inflammatory response that occurs after neutering. Another study showed that beta-1,3-glucan stimulates both adaptive and innate immunity in a species of fish [18]. Beta-1,3-glucans are one of the most abundant polysaccharides in algae [19]. This may suggest that feeding or administering Chlorella or its extract, being a rich source of beta-1,3-glucan [20] can enhance disease resistance in fish. In another study, the immunomodulatory activity of whole blue-green alga in humans and different animals, such as cats and chickens, was described. Because of the high nutritional value of microalgae, application to livestock feed is noted. Jeon et al. (2016) evaluated the dietary effect of lutein-fortified Chlorella on the milk production and components of Holstein cows [21]. In this study, three weeks feeding of conventional (15 g/day) or lutein-fortified Chlorella (30 g/day) [22] increased concentrations of milk protein and solids non-fat without changing milk yield by either feeding of conventional or lutein-fortified Chlorella compared to control. The feeding of lutein-fortified Chlorella increased lutein content in milk compared to conventional Chlorella and control. Lutein is known to have antioxidant properties [23]. Therefore, these results suggest that Chlorella is capable of increasing nutrient components in the milk as well as functional materials, such as antioxidants in dairy products. Similar results were reported by Lammine et al. (2019), however researchers pointed out the necessity of improving microalgae palatability [24]. The application of microalgae for livestock feed is also attempted in pigs [25] broiler chickens [26] goats [27] etc.

FUCOIDAN FROM MACROALGAE IN VETERINARY MEDICINE

Fucoidan a long chain sulfated polysaccharide has been found in various species of brown macroalgae, such as Hizikia fusiformis (Hijiki), Cladosiphon okamuranus (Mozuku), Laminaria japonica (Kombu), Undaria pinnatifida (Wakame) etc. [28]. These brown macroalgae are common food in East Asia and have been cultivated in that area. Multiple medicinal properties of fucoidan have been reported in both human and veterinary medicine [29].

Laura et al. demonstrated that fucoidan extracted from Cladosiphon okamuranus inhibits canine distemper virus (CDV) infection *in vitro* by interference in the early stage of CDV infection and by inhibiting CDV-mediated cell fusion [30]. The cytotoxicity of fucoidan (CC50=2,089 ± 6 µg/ml) was much lower than that by antiviral drug, ribavirin (CC50=88.9 ± 6 µg/ml). Fucoidan treatment (0.1-10 µg/ml) inhibited CDV proliferation in CDV-infected cells. Both pretreatment and simultaneous treatment with various concentrations of fucoidan (0.001–10 µg/ml) inhibited CDV infection into cells. Fucoidan treatment (0.001-10 µg/ml) inhibited cell-cell fusion of CDV-infected cells, which is important mechanisms for cell to cell spread of progeny viruses.

The property of fucoid an as a prebiotic was also investigated in domestic animals [31]. Many researchers evaluated the effect of fucoidan and laminarin on the gut microbiota in piglets. Laminarin is storage form of glucan found in brown algae and known with fucoidan as a mucopolysaccharide. A notable effect of feeding fucoidan and laminarin in combination to sows is the reduction of the gut *Escherichia coli (E. coli*) population in their piglets [32,33]. Leonard et al. (2011) reported that the effect of maternal dietary supplementation with a seaweed extract (10 g/day) composed of 1 g laminarin, 0.8 g fucoidan, and 8.2 g ash on the *E. coli* population in intestinal microbiota of post-weaning piglets. The population of *E. coli* in the caecum and the colon was reduced 16% compared to piglets from the basal diet fed sow at 9 days post wearing. This effect of fucoidan+laminarin on *E. coli* population in piglets was also observed in separate

studies [34, 35]. Since it is well known that *E. coli* have various pathogenic strains and often causes diarrhea to piglets[36] these results strongly suggest that supplementations of fucoidan and/or laminarin are beneficial to piglet health and the industry.

BLUE-GREEN ALGAE (CYANOBACTERIA) IN VETERINARY MEDICINE

Cyanobacteria are Gram-negative bacteria. Algae belong to eukaryotes, while cyanobacteria belong to prokaryotes. Therefore, these are different organisms. However, cyanobacteria share similar features with green algae, such as photosynthetic properties, their habitat, and their color; blue (phycocyanin) and green (chloroplast). Therefore, cyanobacteria are also called as blue-green algae.

Spirulina refers to the biomass of Arthrospira platensis which is one of the species of cyanobacteria. Because of a high nutritional value due to proteins, carbohydrates, fatty acids, vitamins, minerals, etc., whole-spirulina powder or its tablet form is commonly consumed as food supplement for human and animals [37]. In addition, therapeutic properties such as antioxidant [38] antiviral [39] anti-inflammatory and immunomodulating [40] anti-obesity [41] anticancer [42] etc. have been reported. In the veterinary field, the effect of spirulina on the gut microbiota was evaluated in dogs [43] and broiler chickens [44]

On the other hand, hazardous properties of cyanobacteria are reported. Cyanobacterial blooms cause severe damage to organisms inhabiting the environment, and economic activities benefitting the environment [45]. Some of cyanobacteria produce a toxin called cyanotoxin. Microcystin produced by Microcystis aeruginosa is known to cause serious damage to the liver [46]. Saxitoxin produced by Alexandrium catenella is also known as shellfish poisoning, which is caused by shellfish that ate cyanobacteria with their toxin. This is also harmful for livestock, poultry, and pets [47]. In the case of dogs, symptoms appear after exposure to freshwater with cyanobacterial blooms [48, 49].

POTENTIAL BENEFITS OF CHLORELLA IN HUMAN AND VETERINARY MEDICINE

One microalgae that has recently become popular among the microalgae populations is Chlorella, a single-celled green algae renowned for its highly nutritious and commercial benefits [50]. Chlorella in one genus of microalga living in fresh water. The genus of Chlorella is composed of more than 20 species and the species are further divided into three varieties: C. vulgaris, C. lobophora, and C. sorokiniana [51]. Chlorella has potential protective functions such as immunostimulatory, anticancer, anti-inflammatory, antiviral, antimicrobial, anti-fungal, anti-diabetic, anti-hypercholesterolemic, and anti-atherosclerotic effects, among others, as have been described [51]. Being a natural and less expensive source, Chlorella and its extracts could potentially provide a good supplement or alternative to more expensive conventional therapies which may also have high incidence of side effects in treatment of animals. There is a definite need for more research to further evaluate the potential benefits that could be derived from Chlorella and other valuable microalga in companion, production, and other categories of animals as a step towards improving animal health, production, and welfare. Studies should also be conducted to determine safety and tolerance levels in different species as there have been reports of side effects in humans, such as allergies, nausea, vomiting, and other gastrointestinal problems [52] as well as acute tubulointerstitial nephritis [53].

LPS-LIKE MOLECULE IN CHLORELLA

Bacterial lipopolysaccharide (LPS) is an endotoxin found in the cell wall of gram-negative bacteria. It shows various bioactivities in human and animals *via* cell surface receptor, Toll-like receptor 4 (TLR4). LPS stimulates antigen presenting cell proliferation and induces the secretion of pro-inflammatory cytokines from them. In the Chlorella species, the presence of a LPS-like molecule in the cell wall of Chlorella has been demonstrated using immunohistochemical techniques [54]. In a recent study, our research team demonstrated that a bioactive factor partially purified from the isolated cell wall membrane fraction of Chlorella sorokiniana (Chlorella membrane factor, abbreviated as CMF) attenuated the growth of colon carcinoma *via* an alteration of host anticancer immunity [55]. The CMF showed opposite effects compared to bacterial LPS on the CT26 murine colon carcinoma cell growth, in which CMF attenuates cell growth, whereas the LPS stimulates the growth of the cancer cells. It is, therefore, suggested that the action of CMF is functionally different from bacterial LPS in stimulation of cancer cell growth. On the other hand, CMF showed an immune stimulating effect in cell culture and mouse. In the study with the three-dimensional cancer spheroid co-culturing with T lymphocytes, CMF stimulated functional differentiation of T lymphocytes, thereby inhibiting growth of colon carcinoma cells. In a mouse study, the intraperitoneal administration of CMF (10 or 30 mg/kg) was carried out using CT26 cell intraperitoneal dissemination mouse model. The analysis of immune cell population in the mouse ascites, CD4+, CD8+, and CD19+ T cell populations were particularly increased, while CD68+ macrophage population was decreased in ascites in the mice treated with 30 mg/kg CMF. The LY6G+ granulocyte (neutrophil) population in ascites was also decreased in mouse groups treated with 10 or 30 mg/kg CMF. These two cell populations, macrophages and neutrophils, were known to participate in tumor growth [56,57]. Therefore, these results suggest that CMF treatment cause modulation of anticancer immunity by increasing anti-tumorigenic effector T cells and decreasing pro-tumorigenic immune cell populations. It is also suggested that Chlorella cell wall membrane may be a potential source for novel therapeutics with immunomodulatory properties.

DISCUSSION AND CONCLUSION

In conclusion, early research supports that algae may be a very useful complementary/alternative treatment, applicable to a wide array of medical issues due to its immunostimulatory, anticancer, anti-inflammatory, antiviral, antimicrobial, anti-fungal, anti-diabetic, anti-hypercholesterolemic, and anti-atherosclerotic properties. However, most research regarding the above-described bioactivities has not been rigorously evaluated by traditional pharmacokinetics and pharmacodynamics studies and patient-based clinical trials. The issue of the biosafety is another concern; since many studies have evaluated the bioactivities of algae using whole algae without purification of bioactive components, potential toxic components in microalgae would be higher when the intake of algae increases. Therefore, it is critically important to conduct additional research to evaluate the topic properly.

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