



Incorporation of macroalgae to fish feed lowers allergenic properties in fish: An opinion study

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ABSTRACT

As additional information about the chemistry and function of the food produced and its effects on health becomes available, the concept of a nutritious diet continues to evolve and become more precise. Such foods can be made using marine and terrestrial organisms, such as fish that contain long-chain polyunsaturated fatty acids that exhibit effects and play an important role in health. However, fish consumption has been linked to cases of fish allergy, an IgE-mediated condition that has a prevalence reaching 7% of allergic events. Marine macroalgae – with all their health-promoting properties – have become of interest lately to be used as an alternative ingredient in fish feed that is important to minimize allergens in fish consumption that may be harmful to human health. This opinion is trying to summarize the latest evidence on fish feed fortification with macroalgae as a solution to reduce allergies due to fish consumption. It was highlighted that feeding fish with macroalgae fortification was proven to increase growth, stress resistance, and the immune system of fish, as well as reduce the amount of protein retention associated with the pathophysiology of fish allergy. In addition, in the development of the use of macroalgae, it is also expected that in vitro and in vivo research will also be carried out to prove the provision of fish feed with macroalgae related to fish allergies and focus on producing macroalgae formulations that are suitable for application as fish feed to prevent or reduce the incidence of fish allergy in humans.

1. Introduction

As additional information on the chemistry and function of manufactured food and its effects on health becomes available, the concept of a nutritious diet is continually evolving and becoming more precise [1]. A significant amount of research data indicates that healthy dietary habits have a favorable impact on health and can lower the occurrence of non-communicable ailments. Such foods can be created using both sea and land-based organisms. Among these, fish contain long-chain polyunsaturated fatty acids which exhibit anti-inflammatory effects, reduce

blood clotting, and play essential roles in regulating cell membranes and the proper functioning of the cardiovascular, brain, and nervous systems [2]. Fish is considered a superfood because it contains high levels of polyunsaturated omega-3 fatty acids, bioactive peptides, amino acids, vitamin D, selenium, phosphorus, and calcium. These nutrients are known to have health-promoting effects when consumed [2]. Fish, as a main source of protein, plays a crucial role in meeting the dietary needs of millions of people worldwide. With their high-quality protein content, essential amino acids, and various vitamins and minerals, fish are considered a valuable food source that contributes to human health and

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nutrition. Moreover, fish are incredibly diverse, occupying a wide range of water habitats, including freshwater, marine, and brackish environments; implying a flexibility to be cultured. However, fish consumption has been linked with fish allergy, an Ig E-mediated condition that can have a prevalence of up to 7% [3]. The interpretation of serum IgE test results is highly dependent on the allergen content, potency, and stability of the allergen extract [4]. Adverse reactions to seafood can be classified into 3 categories, based on the mechanisms involved: (1) immunological reactions, including IgE and non-IgE allergic reactions such as food protein-induced enterocolitis syndrome; (2) toxic reactions, including marine biotoxins; and (3) food intolerance.

Interestingly, macroalgae – another marine food source – may bring an answer to these issues. Macroalgae have been widely applied in human food, pharmaceuticals, and agriculture [5]. The components found in seaweed can aid in maintaining good gut health and reducing the risk of obesity and diabetes. Additionally, they possess antiviral, anticancer, and anticoagulant properties, all of which are important factors in preventing and treating non-communicable diseases [6]. On the other hand, antioxidants may play a key role in reducing the risk of allergic disease [7]. Macroalgae are rich in phenolic molecules with numerous therapeutical benefits mainly antioxidants, and these health benefits are also projected to be beneficial for fish and livestock [8]. Macroalgae, also present an innovative and valuable dietary component in fish diets. These macroalgae are regarded as an environmentally friendly feed ingredient because they can be produced without depending on costly farmland, as they can be gathered from coastal areas or cultivated. It has also been documented that incorporating macroalgae into fish diets leads to improvements in fish growth, physiology, stress resilience, immune system function, and the quality of fillet muscles [9]. Meanwhile, incorporating macroalgae in fish feed offers economic advantages by reducing reliance on expensive arable land, minimizing land acquisition and maintenance costs, and requiring fewer resources compared to traditional crops. It serves as a sustainable alternative to fishmeal and fish oil, reducing dependency on finite resources, stabilizing costs, and positively impacting fish health, growth, and profitability for farmers [9–11]. Macroalgae – with all their health-promoting properties – may then be an important fish feed ingredient due to their anti-allergic and anti-inflammatory properties [12,13]. These effects which modulate the immune response against the allergenic properties of fish are contributed by their fucoidans [14] and sulfated polysaccharides [15] contents. In conjunction with that, the incorporation of macroalgae to fish feed also brings some implications for fish culturing production. This opinion paper presents recent evidence regarding fish feed fortification with macroalgae as a solution to lower allergies caused by fish consumption.

2. Material and methods in terms of search strategy literature for the synthesis of this opinion article

The literature search was conducted by authors from January 1st, 2010, to May 1st, 2023. Several well-established databases were used, including Taylor & Francis, PubMed, CENTRAL, ProQuest, Google Scholar, EBSCO, and ScienceDirect; using keywords: “Algae” AND “Fish Feed” AND “Allergenic Properties” OR “Macroalgae” AND “Immune” AND “Seafood” AND “Fish Allergies”; and without further inclusion and exclusion criteria to synthesize the opinion of this article.

3. Fish and its allergenic properties

Food allergies are immune reactions to certain foodstuffs (called allergens) that affect hundreds of millions of people globally, with 1% of them being adults and 4% being children [16]. Based on the underlying mechanism, adverse reactions to fish allergy can be divided into three groups: 1) Immunological responses, such as allergic responses and Food Protein Induced Enterocolitis Syndrome (FPIES); 2) Toxic responses, such as marine biotoxins; and 3) Food intolerance. Adverse reactions

due to toxins and/or foods mimic the clinical signs of seafood allergy frequently [17]. The small muscle protein parvalbumin (10–13 kDa, pI 4.1–5.2), which has a conserved structure, is the primary fish allergen. It was determined that more than 95% of allergic responses to fish are caused by parvalbumin, the most often identified allergenic fish protein [18]. Fish can trigger serious adverse reactions mediated by immunoglobulin E (IgE) antibodies in sensitized individuals. Specific IgE for fish allergens are Gadcl and Cypcl [19]. Fish allergies can be caused by heat-stable proteins that are not inactivated during cooking [17,20]. In addition, the IgE-mediated protein parvalbumin is highly reactive compared to other antibodies under all conditions [21]. After-meal allergy symptoms can manifest quickly and might vary from urticaria, nausea, and vomiting to asthma attacks and anaphylaxis.

Nonimmunological reactions to seafood must be determined in clinical evaluation in several ways, including IgE trials and oral food challenges (OFCs). IgE testing of specific fish and shellfish allergens will help identify people who are at risk of persistent seafood allergy and severe clinical responses. An effective *in vivo* test to identify food allergies is the OFC, in which several food additives suspected of causing allergies are introduced to the patient to assess their potential to have adverse effects. Patients of any age can undergo OFC, which is particularly helpful if the type of food that causes an adverse reaction is unclear. In managing fish allergy, auto-injectable epinephrine which has been prescribed can be given regarding cross-contamination of allergies [4]. There are several advantages to administering epinephrine, including rapid cessation of most reactions both non-anaphylactic and anaphylactic reactions, can simplify management by suggesting the use of epinephrine for all reactions and demonstrating to patients and families that epinephrine is safe and easy to use, which may promote the use of epinephrine to treat reactions in the future [22].

Non-immune reactive sensitization in fish allergy refers to a form of adverse reaction to fish consumption that does not involve an immune-mediated response [23]. Unlike a traditional fish allergy, which involves the immune system's production of specific antibodies (e.g., IgE) against fish proteins, non-immune reactive sensitization occurs through non-immunological pathways. This type of sensitivity can manifest as adverse symptoms following fish ingestion but without the involvement of the immune system. Several hypotheses regarding mechanisms underlying non-immune reactive sensitization in fish allergy have been proposed. One hypothesis suggests that certain compounds present in fish, such as histamine or other biogenic amines, may trigger adverse reactions in sensitive individuals [24]. These compounds can accumulate in spoiled or improperly stored fish and elicit symptoms such as gastrointestinal distress, headaches, or skin reactions. Another proposed mechanism involves the activation of sensory neurons, which can be triggered by certain molecules in fish, such as trimethylamine oxide (TMAO) [25]. Activation of these neurons can lead to symptoms such as itchiness, flushing, or respiratory distress in susceptible individuals. It is important to differentiate non-immune reactive sensitization from immune-mediated fish allergies, as the diagnostic and management approaches differ. Traditional fish allergies involve immune responses and are typically diagnosed through allergen-specific IgE testing or oral food challenges. In contrast, diagnosing non-immune reactive sensitization can be more challenging, often requiring a detailed history of symptoms and exclusion of other potential causes. Managing non-immune reactive sensitization primarily involves avoiding fish consumption or minimizing exposure to triggers, such as spoiled fish or certain compounds present in fish [23].

4. Current application of macroalgae as a fish feed ingredient

Macroalgae were found to produce a variety of nutrients that can help provide basic nutrients for fish to consume. Until now, there is an increasing trend regarding fish feeding using macroalgae that can increase fish growth, immune system, and stress resistance of cultured fish [9]. Phytochemicals (xanthophylls and carotenoids), polyunsaturated

Table 1
Implications of incorporation of macroalgae to fish feed based on evidence.

No	Author, Year	Study Design	Macroalgae Types	Outcomes	References
1	[27]	Feeding Trial	Green macroalgae <i>Ulva lactuca</i>	The African catfish <i>Clarias gariepinus</i> will experience lower growth performance and feed utilization if the <i>Ulva lactuca</i> composition is $\geq 20\%$.	[27]
2	[28]	Feeding Trial	A mixture of seaweeds (<i>Pterocladia capillacea</i> , <i>Jania rubens</i> , and <i>Ulva lactuca</i>)	Hematological parameters (red blood cells, hemoglobin, hematocrit, and white blood cells) and serum protein profiles (albumin, total protein, and globulin) were significantly improved.	[28]
3	[29]	Feeding Trial	<i>Caulerpa cylindracea</i>	Improves the reproductive performance of fish by affecting the hypothalamic-pituitary-gonadal axis.	[29]
4	[30]	Feeding Trial	<i>Padina australis</i>	Increase feeding intake in <i>Danio rerio</i> . There is an increase in growth index (final weight, length, and rate of weight gain) in fish given <i>Padina australis</i> feed.	[30]
5	[31]	Feeding Trial	<i>Ulva intestinalis</i>	Giving <i>Padina australis</i> extract for eight weeks to goldfish can bolster immunological response, digestive enzyme function, growth performance, and illness resistance against <i>A. hydrophila</i> infection.● Whole body extract which includes total protein levels, globulin levels, and lysozyme activity was found to be increased in the <i>Danio rerio</i> group given <i>Ulva intestinalis</i> . Enhances the regulation of genes associated with the immune system, including lysozyme (Lyz) and interleukin 1 beta (IL-1), as well as genes related to antioxidants (SOD and CAT) and growth, including growth hormone (GH) and insulin-like growth factor I (IGF-1).●	[31]
6	[32]	Feeding Trial	Marine red seaweed (<i>Halymenia dilatata</i>)	<i>Halymenia dilatata</i> improves growth performance, body composition, chemistry, and digestive enzymes in <i>Labeo rohita</i> so that it can be used for fish feed to reduce fish feed production costs.	[32]
7	[33]	Feeding Trial	<i>Halophytys incurva</i>	Increase antioxidants, metabolic enzymes and promote growth and immune response. There was an increase in total protein, total immunoglobulin activity, and lysozyme in whole body serum and increased skin mucus in fish given <i>H. incurva</i> . The administration of <i>H. incurva</i> can regulate tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), and interferon-gamma (INF- γ) so that it will increase immune defense and antioxidants.	[33]

fatty acids (PUFA), including docosahexaenoic acid (DHA), phenolic compounds, tannins, peptides, lipids, enzymes, vitamins, carbohydrates, and terpenoids are among the substances present in algae [26].

Based on Table 1, the use of macroalgae has been widely implemented as a fish feed ingredient with benefits ranging from growth performance, economic cost, preventing diseases, and improving the physiological status of fish. The economic feasibility of incorporating macroalgae into fish feed ingredients has gained significant attention in recent years. As a sustainable and nutrient-rich alternative to traditional feed ingredients such as fishmeal and soybean meal, macroalgae offers potential cost savings and environmental benefits. By reducing the reliance on expensive and finite resources, such as fishmeal, and utilizing macroalgae as a readily available and renewable source, aquaculture operations can potentially lower their production costs. Additionally, macroalgae cultivation and harvesting can be relatively cost-effective, particularly in coastal regions where these organisms naturally thrive. The overall economic feasibility of incorporating macroalgae into fish feed depends on factors such as macroalgae availability, processing costs, market demand for sustainable aquaculture products, and the specific target species [9,34]. Furthermore, the addition of seaweed helped regulate the immune response in fish linked to immune-related enzymes, genes, immunoglobulin, antioxidants, inflammation, and blood and protein profiles.

5. Macroalgal-based fish feed lowers fish allergenic properties

Several studies related to the benefits of macroalgae in fish feed emphasize the benefits of antioxidant and non-protein nitrogen content in the nutrition of these fish. Among marine organisms, macroalgae are one of the high natural sources of antioxidants such as vitamin E, peptides, glutathione peroxidase, superoxide dismutase, ubiquinone, and catalase as well as complete vitamins such as vitamins A, B1, B12, C, D, E, riboflavin, niacin, and folic acid [35]. Macroalgae dietary supplementation has the effect of improving the immune status and fish growth

performance [8]. This will indirectly affect the consumers of these fish. Laminarin, which is typically high in macroalgae, is also reported to downregulate the production of pro-inflammatory mediators and has health-enhancing effects including improved immunological response (promoting lysozyme activity and increasing complement pathway activity), improved antioxidant status, and better ROS response [8,36].

Reducing the prevalence of fish allergy with macroalgae feed can also be based on theories from previous studies, where fish feed with macroalgae, especially the type of green algae *Ulva* spp. has the effect of reducing the amount of protein retention in the fish studied but on the other hand increasing the amount of lipids in fish so that there is an increase in overall body weight [27]. In another study with red macroalgae fish feed such as *P. purpurea* in *Chelon labrosus* fish, it was found that the decrease in net protein utilization was inversely proportional to the increase in the amount of *P. purpurea* consumption given [37]. The main reason why the protein composition in fish consuming macroalgae feed is lower is that the concentration of essential amino acids (EAA) in macroalgae, across the biomass base, is much lower than other fish feed sources such as soybeans and corn, even though these amino acids are one of the raw materials for protein synthesis which affects decreasing protein composition in fish [38]. Theoretically, if the amount of protein deposition in fish decreases, the amount of allergen protein will also decrease, thereby reducing the prevalence of fish allergy incidence in humans. Parvalbumin, specifically the subtype β -parvalbumins, is one of the main proteins in fish meat and is also the main allergen that causes symptomatic symptoms in fish allergy patients [39]. This protein is responsible for 95% of fish allergy incidence through the allergy-mediated IgE pathway beginning with the attachment of the protein's allergen to an antigen-specific T helper 2 cell-inducing cytokine that signals IL-4 response to stimulate B-cells to produce IgE antibodies which will bind to a mast cell or basophil Fc ϵ receptors. This action leads to the degranulation of these effector cells and also the release of histamine and other inflammatory mediators which lead to the clinical manifestations of allergy [40,41]. This parvalbumin protein

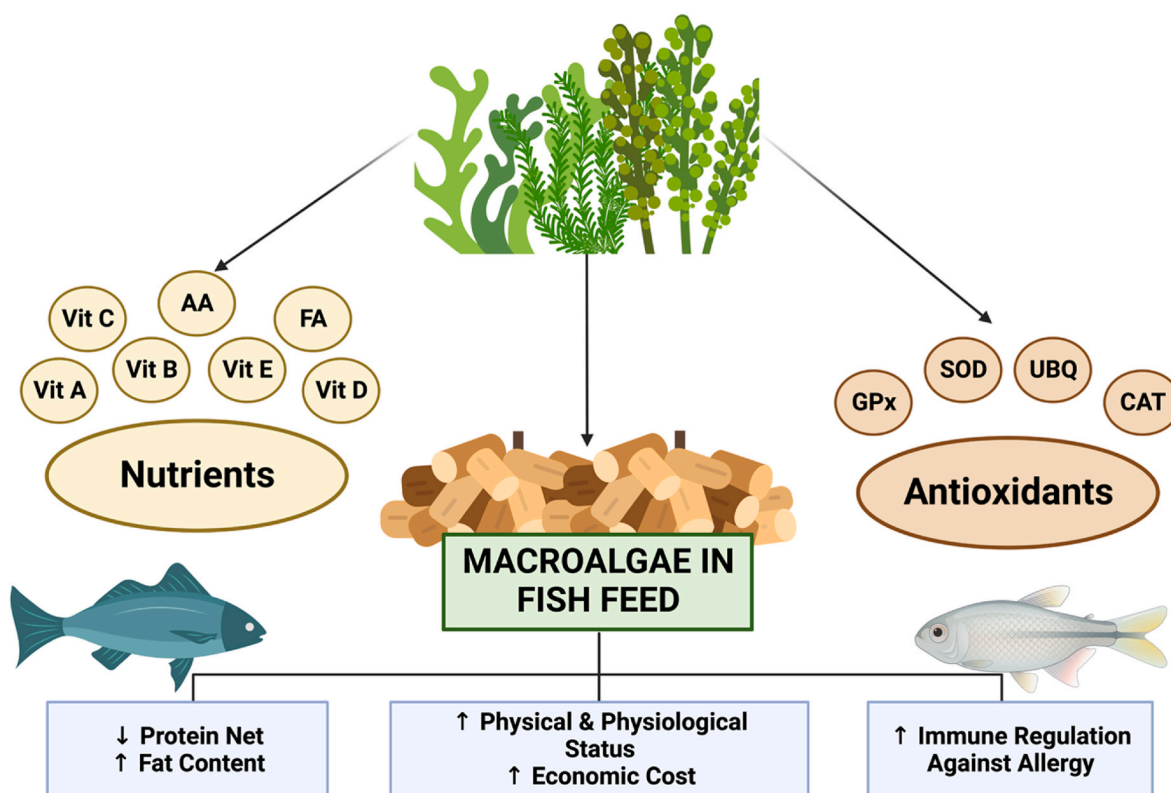


Fig. 1. The incorporation of macroalgae to fish feed lowers allergenic properties in fish.

is usually found in light muscle compared to dark muscle, so active fish with higher amounts of dark muscle are considered fish with low allergen values [42]. Furthermore, macroalgae are also known to exhibit metal chelating activity [43] and IgE binding activity [44], which are the same mechanism with EDTA that has been established to reduce the allergenicity of parvalbumin [45].

Interestingly, as presented in Table 1, the incorporation of macroalgae to fish feed also improves the immunity of fish [28,30–33]. This effect is possibly caused by the vitamins, bioactive compounds (phenolic compounds), fatty acids, and antioxidative compounds retained in the fish. These contents may improve the immune regulation against fish allergies by modulating IL-10 and transforming growth factor beta (TGF- β), the key regulator of T cells and B cells [46]. Furthermore, algal-derived molecules have immunity properties that are considered safe [47]. To sum up, this opinion highlights a new horizon of macroalgae application on fish feed to reduce the allergenic properties in this rich protein source. Graphical Abstract and Fig. 1 present the potential mechanism of macroalgae in lowering the allergenic properties of fish.

6. Future implications and conclusions

Previous studies have highlighted the potential use of macroalgae as a form of prevention of fish allergies, especially in the form of fish feed [48]. Feeding fish with macroalgae fortification is proven to increase growth, stress resistance, and fish immune system, and reduce the amount of protein retention associated with the pathophysiology of fish allergy [9]. These existing effects are potentially contributed by the nutrients and bioactive compounds present in the macroalgae. Furthermore, macroalgae also have antioxidant, anti-inflammatory, and immunostimulant properties [49]. However, research that specifically discusses macroalgae and fish allergies is still very few and inversely proportional to the potential that can be generated from both [50].

Through this opinion article, further clinical research is needed to shed more light on the relationship between macroalgae and fish

allergies given the potential and positive macroalgae trends in recent years [51]. In addition, in the development of the use of macroalgae, it is also expected that in vitro and in vivo research will also be carried out to prove the feeding of fish with macroalgae related to fish allergies [52]. It is also expected that further research can discuss costs, toxicity, and side effects that may occur, to produce macroalgae formulations that are suitable for application as fish feed to prevent or reduce the incidence of fish allergies.

Author contributions

JFM, LM, WBG, MFS, DY, SF, MFN, MS, FN, and AT: Contributed to the conceptualization with the design of the critical opinion study, drafted the manuscript, edited-revised it, and approved the final version of the submitted manuscript. FN and WBG: Software and Visualization. JFM, LM, AT, and FN: Supervision and Formal Analysis. All authors and contributors contributed to the opinion article and approved the submitted version.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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References

- [1] H. Cena, P.C. Calder, Defining a healthy diet: evidence for the role of contemporary dietary patterns in health and disease, *Nutrients* 12 (334) (2020) 1–15, <https://doi.org/10.3390/nu12020334>.
- [2] S.K. Tilami, S. Sampels, Nutritional value of fish: lipids, proteins, vitamins, and minerals, *Revi. Fish. Sci. Aquacult. Taylor & Francis* 26 (2) (2017) 243–253, <https://doi.org/10.1080/23308249.2017.1399104>.
- [3] H. Moonesinghe, et al., Prevalence of fish and shellfish allergy: a systematic review, *Ann. Allergy, Asthma & Immunol. Elsevier* 117 (3) (2016) 264–272.e4, <https://doi.org/10.1016/j.anai.2016.07.015>.
- [4] C.M. Davis, et al., Clinical management of seafood allergy, *J. Allergy Clin. Immunol.: In Practice. Elsevier Inc* 8 (1) (2020) 37–44, <https://doi.org/10.1016/j.jaip.2019.10.019>.
- [5] A. Leandro, L. Pereira, A.M.M. Gonçalves, Diverse applications of marine macroalgae, *Mar. Drugs* (2020), <https://doi.org/10.3390/md18010017>.
- [6] E.S. Brown, et al., Seaweed and human health, *Nutr. Rev. United States* 72 (3) (2014) 205–216, <https://doi.org/10.1111/nure.12091>.
- [7] H. Rosenlund, et al., Antioxidant intake and allergic disease in children, *Clin. Exp. Allergy: J. British Soc. Allergy and Clin. Immunol. England* 42 (10) (2012) 1491–1500, <https://doi.org/10.1111/j.1365-2222.2012.04053.x>.
- [8] M.A.E. Naiel, et al., 'Beneficial Impacts and Health Benefits of Macroalgae Phenolic Molecules on Fish Production', *Aquaculture*, vol. 534, Elsevier B.V., 2021, 736186, <https://doi.org/10.1016/j.aquaculture.2020.736186>.
- [9] A.H.L. Wan, et al., Macroalgae as a sustainable aquafeed ingredient, *Rev. Aquacult.* 11 (3) (2019) 458–492, <https://doi.org/10.1111/raq.12241>.
- [10] P.J.G. Henriksson, et al., Interventions for improving the productivity and environmental performance of global aquaculture for future food security, *One Earth* 4 (9) (2021) 1220–1232, <https://doi.org/10.1016/j.oneear.2021.08.009>.
- [11] P. Thornton, H. Gurney-Smith, E. Wollenberg, Alternative sources of protein for food and feed, *Curr. Opin. Environ. Sustain.* 62 (2023), 101277, <https://doi.org/10.1016/j.cosust.2023.101277>.
- [12] S.-K. Kim, T.-S. Vo, D.-H. Ngo, Antiallergic benefit of marine algae in medicinal foods, in: S.-K.B.T.-A. Kim, F. N. R (Eds.), *Advances in Food and Nutrition Research*, Academic Press, 2011, pp. 267–275, <https://doi.org/10.1016/B978-0-12-387669-0.00021-1>.
- [13] T.-S. Vo, D.-H. Ngo, S.-K. Kim, 'Potential targets for anti-inflammatory and anti-allergic activities of marine algae: an overview', *Inflammation & Allergy Drug Targets*, United Arab Emirates 11 (2) (2012) 90–101, <https://doi.org/10.2174/187152812800392797>.
- [14] T.S. Vo, The role of algal fucoidans in potential anti-allergic therapeutics, *Int. J. Biol. Macromol.* 165 (2020) 1093–1098, <https://doi.org/10.1016/j.ijbiomac.2020.09.252>.
- [15] M.R. Soto-Vásquez, et al., FTIR characterization of sulfated polysaccharides obtained from macrocystis integrifolia algae and verification of their antiangiogenic and immunomodulatory potency in vitro and in vivo, *Mar. Drugs* (2023), <https://doi.org/10.3390/md21010036>.
- [16] A. Elghoudi, H. Narchi, Food allergy in children—the current status and the way forward, *World J. Clin. Pediatr.* United States 11 (3) (2022) 253–269, <https://doi.org/10.5409/wjcp.v11.i3.253>.
- [17] T. Ruethers, et al., Seafood allergy: a comprehensive review of fish and shellfish allergens, *Mol. Immunol.* 100 (April) (2018) 28–57, <https://doi.org/10.1016/j.molimm.2018.04.008>.
- [18] A. Kuehn, et al., Fish allergens at a glance: variable allergenicity of parvalbumins, the major fish allergens, *Front. Immunol.* (2014), <https://doi.org/10.3389/fimmu.2014.00179>.
- [19] M.F. Sharp, A.L. Lopata, Fish allergy, *Clin. Rev. Allergy Immunol.* 46 (3) (2014) 258–271, <https://doi.org/10.1007/s12016-013-8363-1>.
- [20] H. Kubota, et al., Reduction in IgE reactivity of Pacific mackerel parvalbumin by heat treatment, *Food Chem. 206* (2016) 78–84, <https://doi.org/10.1016/j.foodchem.2016.03.043>.
- [21] M.F. Sharp, et al., IgE and IgG4 epitopes revealed on the major fish allergen Lat c 1, *Mol. Immunol.* 131 (2021) 155–163, <https://doi.org/10.1016/j.molimm.2020.12.033>.
- [22] T.E. Dribin, S. Wasserman, P.J. Turner, Who needs epinephrine? Anaphylaxis, autoinjectors, and parachutes, *J. Allergy Clin. Immunol.: In Practice. Elsevier* 11 (4) (2023) 1036–1046, <https://doi.org/10.1016/j.jaip.2023.02.002>.
- [23] J.L. Turnbull, H.N. Adams, D.A. Gorard, 'Review article: the diagnosis and management of food allergy and food intolerances', *Alimentary Pharmacology & Therapeutics*, John Wiley & Sons, Ltd 41 (1) (2015) 3–25, <https://doi.org/10.1111/apt.12984>.
- [24] L. Prester, Biogenic amines in fish, fish products and shellfish: a review, *Food Addit. Contam. Part A. Taylor & Francis* 28 (11) (2011) 1547–1560, <https://doi.org/10.1080/19440049.2011.600728>.
- [25] O.B. Adedeji, et al., Benefits, public health hazards and risks associated with fish consumption, *New York Sci. J.* 5 (9) (2012) 33–61.
- [26] E.S. Biris-Dorhoi, D. Michiu, C.R. Pop, A.M. Rotar, M. Tofana, O.L. Pop, S.A. Socaci, A.C. Farcas, Macroalgae-A sustainable source of chemical compounds with biological activities, *Nutrients* 12 (10) (2020 Oct 11) 3085, <https://doi.org/10.3390/nu12103085>. PMID: 33050561; PMCID: PMC7601163.
- [27] A.W.A. Abdel-Warith, E.S.M.I. Younis, N.A. Al-Asghar, Potential use of green macroalgae *Ulva lactuca* as a feed supplement in diets on growth performance, feed utilization and body composition of the African catfish, *Clarias gariepinus*, *Saudi J. Biol. Sci. King Saud Univ.* 23 (3) (2016) 404–409, <https://doi.org/10.1016/j.sjbs.2015.11.010>.
- [28] A.F. Abdelhamid, et al., Potential effects of dietary seaweeds mixture on the growth performance, antioxidant status, immunity response, and resistance of striped catfish (*Pangasianodon hypophthalmus*) against *Aeromonas hydrophila* infection, *Fish Shellfish Immunol.* 119 (2021) 76–83, <https://doi.org/10.1016/j.fsi.2021.09.043>.
- [29] V. Schiano, et al., An alkaloid from a highly invasive seaweed increases the voracity and reproductive output of a model fish species, *Mar. Drugs* (2022), <https://doi.org/10.3390/md20080513>.
- [30] N. Sheikhzadeh, et al., Brown seaweed (*padina australis*) extract can promote performance, innate immune responses, digestive enzyme activities, intestinal gene expression and resistance against *aeromonas hydrophila* in common carp (*Cyprinus carpio*), *Animals* (2022), <https://doi.org/10.3390/ani12233389>.
- [31] E. Rouhani, et al., A. n J, in: Hern ndez Hindawi (Ed.), 'Effect of Dietary Administration of Green Macroalgae (*Ulva Intestinalis*) on Mucosal and Systemic Immune Parameters, Antioxidant Defence, and Related Gene Expression in Zebrafish (*Danio rerio*)', *Aquaculture Nutrition*, 2022, 7693468, <https://doi.org/10.1155/2022/7693468>, 2022.
- [32] D.B. Manikandan, et al., Exploration of marine red seaweed as a dietary fish meal replacement and its potentiality on growth, hematological, biochemical, and enzyme activity in freshwater fish *Labeo rohita*, *Trop. Anim. Health Prod.* 54 (6) (2022) 395, <https://doi.org/10.1007/s11250-022-03392-4>.
- [33] S.H. Hosenifar, et al., Dietary red macroalgae (*Halopithys incurva*) improved systemic mucosal immune and antioxidant parameters and modulated related gene expression in zebrafish (*Danio rerio*), *Fish Shellfish Immunol.* 123 (2022) 164–171, <https://doi.org/10.1016/j.fsi.2022.02.047>.
- [34] K. Hua, et al., The future of aquatic protein: implications for protein sources in aquaculture diets, *One Earth* 1 (3) (2019) 316–329, <https://doi.org/10.1016/j.oneear.2019.10.018>.
- [35] A. Kheiri, J. Aliakbarlu, R. Tahmasebi, Antioxidant potential and fatty acid profile of fish fillet: effects of season and fish species, *Vet. Res. Forum* 13 (1) (2022) 91–99, <https://doi.org/10.30466/vrf.2021.526596.3153>.
- [36] T. Morais, et al., Seaweed potential in the animal feed: a review, *J. Mar. Sci. Eng.* (2020) 1–24, <https://doi.org/10.3390/JMSE8080559>.
- [37] M. Överland, L.T. Mydland, A. Skrede, Marine macroalgae as sources of protein and bioactive compounds in feed for monogastric animals, *J. Sci. Food Agric.* 99 (1) (2019) 13–24, <https://doi.org/10.1002/jsfa.9143>.
- [38] G. Marinho, et al., The IMTA-cultivated Chlorophyta *Ulva* spp. as a sustainable ingredient in Nile tilapia (*Oreochromis niloticus*) diets, *J. Appl. Phycol.* 25 (5) (2013) 1359–1367, <https://doi.org/10.1007/s10811-012-9965-3>.
- [39] X. Jiang, Q. Rao, Effect of processing on fish protein antigenicity and allergenicity, *Foods* (2021), <https://doi.org/10.3390/foods10050969>.
- [40] B. Buyuktiyaki, et al., 'Ige-mediated Fish Allergy in Children', *Medicina (Lithuania)*, 2021, pp. 1–22, <https://doi.org/10.3390/medicina57010076>.
- [41] T. Kalic, et al., Fish allergy around the world—precise diagnosis to facilitate patient management, *Front. Allergy* 2 (October) (2021) 1–16, <https://doi.org/10.3389/falgy.2021.732178>.
- [42] J. Klueber, et al., Fish allergy management: from component-resolved diagnosis to unmet diagnostic needs, *Curr. Treatment Option. Allergy* (2019) 322–337, <https://doi.org/10.1007/s40521-019-00235-w>.
- [43] S. Yarnpakdee, S. Benjakul, T. Senphan, Antioxidant activity of the extracts from freshwater macroalgae (*Cladophora glomerata*) grown in Northern Thailand and its preventive effect against lipid oxidation of refrigerated eastern little tuna slice, *Turk. J. Fish. Aquat. Sci.* 19 (3) (2018) 209–219.
- [44] Y. Li, et al., Brown algae carbohydrates: structures, pharmaceutical properties, and research challenges, *Mar. Drugs* (2021), <https://doi.org/10.3390/md19110620>.
- [45] D. Schrama, et al., Fish allergenicity modulation using tailored enriched diets—where are we? *Front. Physiol.* 13 (2022) 1–8. Available at: <https://www.frontiersin.org/articles/10.3389/fphys.2022.897168>.
- [46] O. Palomares, et al., Regulatory T cells and immune regulation of allergic diseases: roles of IL-10 and TGF- β , *Gene Immun.* 15 (8) (2014) 511–520, <https://doi.org/10.1038/gene.2014.45>.
- [47] F. Nurkolis, et al., Algal-derived macromolecules and their composites: from synthetic biology to biomedical applications in bone and cardiovascular tissue engineering [version 1; peer review: awaiting peer review], *F1000Res.* (65) (2023) 12, <https://doi.org/10.12688/f1000research.129725.1>.
- [48] H.H.E. Saleh, Review on use of macro algae (seaweed) in fish nutrition, *J. Zool. Res. (Aligarh)* 2 (2) (2020) 6–11, <https://doi.org/10.30564/jzr.v2i2.2054>.
- [49] V. Thépot, et al., Meta-analysis of the use of seaweeds and their extracts as immunostimulants for fish: a systematic review, *Rev. Aquacult. John Wiley Sons*, Ltd 13 (2) (2021) 907–933, <https://doi.org/10.1111/raq.12504>.

- [50] C.A. James, S. Welham, P. Rose, Edible algae allergenicity – a short report, *J. Appl. Phycol.* 35 (1) (2023) 339–352, <https://doi.org/10.1007/s10811-022-02880-2>.
- [51] E.-S. Biris-Dorhoi, et al., Macroalgae—a sustainable source of chemical compounds with biological activities, *Nutrients* (2020), <https://doi.org/10.3390/nu12103085>.
- [52] M. Luijten, et al., 'Relevance of in vitro transcriptomics for in vivo mode of action assessment', *chemical Research in toxicology*, Am. Chem. Soc. 34 (2) (2021) 452–459, <https://doi.org/10.1021/acs.chemrestox.0c00313>.