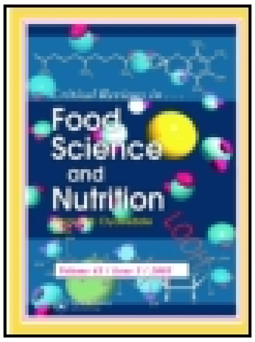

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REVIEW

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Can human nutrition be improved through better fish feeding practices? a review paper

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ABSTRACT

Achieving Sustainable Development Goal 2 of zero hunger and malnutrition by 2030 will require dietary shifts that include increasing the consumption of nutrient dense foods by populations in low- and middle-income countries. Animal source foods are known to be rich in a number of highly bioavailable nutrients that otherwise are not often consumed in the staple-food based diets of poorer populations throughout the world. Fish is the dominant animal source food in many low- and middle-income countries in the global south and is available from both fisheries and aquaculture. Consumers often perceive that wild caught fish have higher nutritional value than fish produced through aquaculture, and this may be true for some nutrients, for example omega-3 fatty acid content. However, there is potential to modify the nutritional value of farmed fish through feeds and through production systems, illustrated by the common practice of supplementing omega-3 fatty acids in fish diets to optimize their fatty acid profile. This manuscript reviews the evidence related to fish feeds and the nutritional composition of fish with respect to a number of nutrients of interest to human health, including iron, zinc, vitamins A and D, selenium, calcium, and omega-3 fatty acids, with low- and middle-income country populations in mind. In general, we find that the research on fortification of fish diet particularly with vitamins and minerals has not been directed toward human health but rather toward improvement of fish growth and health performance. We were unable to identify any studies directly exploring the impact of fish feed modification on the health of human consumers of fish, but as nutrition and health rises in the development agenda and consumer attention, the topic requires more urgent attention in future feed formulations.

KEYWORDS
fish; aquaculture; essential nutrient; muscle; flesh; nutritional deficiency; feed; diet; functional food

Introduction

The contribution of aquaculture to food security

Hunger and malnutrition remain major global problems despite progress in recent years. According to the Food and Agriculture Organization of the United Nations (Fisheries FAO, 2018) approximately 11% of the world population suffers from poverty and lack of access to sufficient nutritious food necessary for human health. The estimated number of people who suffer from chronic hunger declined by 17% from 1990-92 until 2015, but according to the most recent reports global hunger is on the rise again, affecting 815 million people in 2016. The current plan to reduce hunger and malnutrition by 2030 focuses primarily on development of sustainable agriculture and food systems to ensure food supply stability and access to adequate health and nutrition (Fisheries FAO, 2017).

There has been a major growth in food production in the past decades. Almost one billion people, however, still have no access to sufficient nutritious food necessary for human health (Fisheries FAO, 2018). It is estimated that by 2050, population growth in developing countries in South Asia and sub-Saharan Africa will increase by 2.4 billion people, many who will depend on agriculture for livelihoods (Lipper et al. 2014). At the same time, limitations on agricultural land, partly due to urbanization, salinization, and desertification, impose a major challenge for sustainable food production systems (Godfray et al. 2010). Moreover, the overexploitation of natural resources and the impact of climate change with extensive fluctuations in rainfall and drastic temperature shifts risks further impacts on crop production systems and agriculture and aquatic biodiversity (Lipper et al. 2014). The continued development of food production systems that will be able to sustain human demands for health and nutrition will depend on advancing innovative production systems with lower energy requirements that pose less stress on land and freshwater (Navarro et al. 2012) as well as changes in consumption and dietary trends.

Aquaculture and fisheries are both seen as key to the future of food production, health, and nutritious food systems (Waite et al. 2014). With FAO reporting many

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fisheries being fully exploited or overfished (Fisheries FAO, 2018), aquaculture is an increasingly important source of fish, including in less developed countries (Belton, Bush, and Little 2016). Currently, fish provide approximately 3.2 billion people with almost 20 percent of their average per capita intake of animal protein and these values are still on the rise (Fisheries FAO, 2018; Godfray et al. 2010). The 2013 "Fish to 2030: Prospects for Fisheries and Aquaculture" World Bank report predicted that 62% of fish provided by aquaculture for human consumption will be delivered by 2030 mostly from fish species including: carp, catfish, and tilapia - for which the global yield is expected to rise from 4.3 million tons to 7.3 million tons between 2010 and 2030.

Aquaculture feeds

The global fisheries production exceeded 171 million tonnes in 2016 (Fisheries FAO, 2016). From that, the amount of fish used for direct human consumption has increased significantly in recent decades, from 67% in the 1960s to 88% in 2016. (Fisheries FAO 2016). The remaining 12% (~20 million tonnes) in 2016 was used for non-food products mainly for fishmeal and fish oil production (Fisheries FAO 2018). Fishmeal is a high protein powder derived from the industrial processing of small pelagic fish (e.g. anchovy, sardine, capelin, herring, etc.). For decades fishmeal has been one of the major ingredients in feeds for fish and livestock due to its high quality, highly digestible protein, optimal essential and non-essential amino acids, fatty acids, and micronutrient composition (Merino et al. 2012). It has been predicted, however that the future of aquaculture will depend on human capacity to continuously reduce the reliance on raw materials of marine origin with plant-based products and other ingredients from rendered animal sources and animal waste. Significant amounts of fishmeal and fish oil have been successfully replaced with alternative ingredients derived mainly from commodity agricultural crops. Those include high-quality plant protein concentrates such as soy/pea protein concentrate, wheat/corn gluten, as well as lower-quality plant protein sources such as soybean meal, sunflower expeller, distillers dried grains with solubles, cottonseed meal, etc. A vast amount of research has been carried in order to reduce the amount of fishmeal and fish oil in animal feeds and the dietary formulations of commercial diets produced today deviate substantially from formulations introduced to the aquaculture market decades ago (Delamare-Deboutteville et al. 2019, Kwasek et al. 2011; Blasco, Fondevila, and Guada 2005; Elangovan and Shim 2000; Øverland and Skrede 2017; Espe et al. 2006, 2007; Hansen et al. 2007; Helland and Grisdale-Helland et al. 2006). The use of vegetable meals and oils (e.g., soy, corn, canola, palm, sunflower oils) in place of fishmeal and fish oil, respectively, have been noted to impair nutritional properties of farmed seafood by reducing for example the levels of certain omega-3 (n-3) fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). However, the effect of these changing fish diets on nutritional values of fish and human health and nutrition remain understudied (Fry et al. 2016; Sapkota et al. 2007).

Nutritional characteristics of fish and health benefits of fish consumption

More than two billion people in the world are estimated to suffer from micronutrient deficiencies, although considerable uncertainty exists around this estimate (Tacon and Metian 2013). Poor growth in children may be a function of dietary inadequacies during early childhood (energy, protein, and micronutrients) but also may be caused by exposure to infectious diseases and prenatal nutritional inadequacies or exposures (Neumann, Harris, and Rogers 2002).

Fish is often described as a protein, and perhaps for this reason, the role of fish in human nutrition is often centered around its protein content. Like other animal source foods such as eggs, milk, and meat, fish has high protein quality and its digestibility exceeds 90% (Kijora et al. 2006). Protein deficiency was once considered to be a major cause of nutritional problems globally, although interest waned in the mid 1970's with the publication of a manuscript that questioned its importance (Mclaren 1974). In recent years however, the lack of high-quality protein in the diets of young children has been raised as a potential cause of stunting (Semba et al. 2016), rekindling an interest in animal sourced foods.

Certain types of fatty fish are a rich source of long chain polyunsaturated omega-3 fatty acids (PUFA) including EPA and DHA (Deckelbaum and Torrejon 2012). Major sources of the PUFA in many populations traditionally have been fish and fish oils, the supply of which is not sufficient to provide the recommended intake levels of these nutrients for growing human populations. Therefore, attempts have been made by the agriculture industry to "boost" omega-3 fatty acid content of other products, including milk, eggs and poultry meat. While humans have the ability to synthesize these long chain fatty acids by elongating shorter chain fatty acids such as alpha-linolenic acid (ALA), the process is believed to be inefficient (Deckelbaum and Torrejon 2012). Most studies on the relationship between PUFA and health outcomes have been conducted in high income settings where overall nutritional status is presumed to be better. Poor EPA and DHA status in pregnancy has been linked to higher risk of early preterm birth (<34 weeks) (Olsen et al. 2018) and trials of omega-3 supplementation have also shown an overall benefit for this outcome in meta-analysis (Kar et al. 2016). Consumption of long chain omega-3 PUFA in pregnancy is also known to be linked with improved cognitive development scores (Swanson, Block, and Mousa 2012). Many studies, largely conducted in high income settings have also found associations between consumption of fatty fish and/or supplementation with long chain omega-3s and reduced risk of myocardial infarction and coronary heart disease, although heterogeneity in these findings exists (Hu et al. 2006; Zheng et al. 2012).

There is also increasing attention in low- and middle-income settings around the importance of fish in providing micronutrients to populations at risk of deficiency.

Considerable variation may exist in the micronutrient content of fish depending on species, the environment in which they live, whether they are wild caught or farmed, and other characteristics (Hicks et al. 2019). Of the 2000 wild caught species from the sea commonly consumed by humans, however, nutritional analysis has only been conducted in about 350, leaving significant uncertainty around the nutritional value of fish globally (Hicks et al. 2019). Recent efforts to model the nutritional characteristics of marine fish based on ecological characteristics have enabled the estimation of nutritional value for species not yet assessed (Hicks et al. 2019). There have also been some recent efforts to compare the micronutrient and fatty acid content of certain wild-caught vs. farmed species in countries such as Bangladesh (Bogard et al. 2015). Although not studied extensively, findings from a study in Bangladesh, suggest that despite growing fish consumption, largely sourced from aquaculture, micronutrient intake from fish may be declining due to poorer nutritional composition of the consumed parts of farmed fish compared with wild caught fish that once formed the majority of fish consumed (Bogard et al. 2017). These findings suggest the importance of considering feeds, farming practices, and species composition, as elements of nutrition policy in countries where consumption of farmed fish is high. In a world where nutritious and healthy food products are essential, fish and seafood represent a critical component of the global food basket (Tacon and Metian 2013).

Fish as functional food

For many poorer populations throughout the world, fish has long played an important role in providing a food-based source of nutrients that are otherwise difficult to access in food systems. These include key micronutrients known to be more concentrated and/or bioavailable from animal source foods (iron, zinc, vitamin A, vitamin B12, calcium) as well as protein and essential fatty acids (Thilsted et al. 2016). For populations in Africa and South Asia, where fish traditionally came from wild caught sources (either marine or inland), farmed fish is increasingly becoming available and consumed by poor populations (Bogard et al. 2017). This raises important questions about the nutritional content of that fish, and specifically whether farmed fish should be considered a 'functional food'. Functional foods are food products specifically designed to deliver nutritionally valuable component(s) (essential macronutrient or micronutrient) able to amend body functions and decrease the risk of certain diseases (Gormley 2013; Roberfroid 2002). And therefore, functional foods have the potential to minimize medical care costs while improving health and wellness, and giving consumers greater control over their health by providing a convenient form of health-enhancing food. Given the diversity of interactions that exist among nutrient and non-nutrient compounds, the interactive effects of these compounds must be fully elucidated in order to develop functional foods with the greatest potential to synergistically impact the human well-being (Crowe and Francis 2013). Roberfroid (2000) provided five approaches for development of functional food which include: 1) removal of a dietary constituent that is harmful for health, 2) supplementation of a food constituent that is not naturally present and has beneficial effect on health, 3) substitution of a dietary constituent which intake at higher levels might be harmful with a component that has beneficial effect on health, 4) an increase of bioavailability or stability of a food constituent that is beneficial for health, and finally 5) an increase in the amount of naturally occurring (inherently functional) constituent to a level that will have beneficial effect on health. Functional foods seem to have more health benefits relative to regular foods although it needs to be emphasized that many of the regular foods, including both animal and plant products, are beneficial for health 'as consumed' due to their "inherent functionality" (Gormley 2010).

The nutritional content of fish muscle varies as it can be affected by species type and the physiological state of an animal including age, sexual maturity degree, size (Soccol and Oetterer 2003) and by various genetic, environmental (oxygen concentration, photoperiod, temperature, or pH; Johnston et al. 2003, 2006; Wilkes et al. 2001) and nutritional factors (dietary protein source and quality, and dietary amino acid/fatty acid composition) (Steffens 1997; Yıldız et al. 2018; Wijekoon, Parrish, and Mansour 2014). Moreover, the evidence indicates that the quality of animal-based food products is associated with animal feeding practices (Sapkota et al. 2007). Fry et al. (2016) first proposed a conceptual framework which illustrated potential connections between currently used raw materials in aquaculture feed and their effect on environmental health and human nutrition. However, it is unclear how much evidence exists on the potential benefits of modifying fish feed and potential human outcomes. The objective of the present paper was to review the current state of knowledge on enhancement of fish nutritional quality by modification of fish feed formulations with some of the critical nutrients that are necessary for proper human health with particular focus on populations of low- and middle-income countries.

Materials and methods

Search strategy and study selection

Numerous studies have been undertaken on the effects of dietary nutrient supplementation on fish growth, development, and health. However, comparatively less research has been undertaken to explore the link between fortification of fish feeds and direct or indirect effects on human health. The review was conducted using comprehensive searches of the literature using ISI Web of Knowledge, PubMed, as well as conventional browsing tools such as Google Scholar to broaden the spectrum of the search. Search terms (keywords) included the name of a specific nutrient (i.e. iron, vitamin A, calcium, etc.), fish species, diet/feed, human health, functional food, and/or food fortification.

The contents of papers were reviewed and selected based on their direct or indirect relevance to the present review. Two reviewers assessed the inclusion of articles independently. Any additional references found along the process in some of the selected papers relevant to the content of the review were also included. Some studies were also rejected if the project design was considered questionable and posed a risk of introducing biased information. Some nutrient requirement levels are mentioned in the study where applicable or as an example. However, the focus of this review was not on fish nutritional requirements, for which an abundance of research already exists (National Research Council 2011).

Results

Vitamin A

In humans, vitamin A plays an essential role in immune function, growth, and vision (Sommer and West 1996). Vitamin A deficiency remains an important cause of child mortality and child blindness (xerophthalmia) in low- and middle-income countries, although many countries have biannual vitamin A supplementation programs throughout the world targeting children 6-59 months of age (West 2003; Imdad et al. 2017). Humans are able to convert provitamin-A carotenoids, available from orange and yellow fruits and vegetables and from green leafy vegetables, to retinol (Olson, 1989). However, the efficiency of this process is variable and depends on many factors including the food matrix, food preparation, consumption of dietary fat, and even genetic factors (Olson, 1989). In contrast, preformed retinol from animal source foods has greater absorption and bioavailability.

In fish, vitamin A is an essential micronutrient that is incorporated directly from the diet or metabolized from carotenoids. Vitamin A has been indicated to play an important role as an immunostimulant and has a particularly beneficial use in fish farming (Cuesta et al. 2002). Rønnestad, Helland, and Lie (1998) suggested that Atlantic halibut *Hippoglossus hippoglossus* larvae are not able to efficiently convert carotenoids into retinal and/or retinol during the first period after onset of exogenous feeding. Moren, Naess, and Hamre (2002) reported that increasing levels of carotenoids in the diets were reflected in increasing levels of vitamin A in Atlantic halibut *Hippoglossus hippoglossus* whole body and liver tissue which seems to be the storage organ of vitamin A in fish along fish eye which is also found to be an organ significantly contributing to whole body vitamin A content (Hemre et al. 2004). In juvenile sea bream *Chrysiphrys major* different vitamin A supplemental levels had no effect on crude protein, lipid, moisture, and ash contents in the whole body. Fish that received no or low level of vitamin A (300 RE/kg diet) showed no other signs of deficiency except reduced growth. The authors did not report any hypervitaminosis symptoms and argued this was caused by short dietary exposure. Signs of excess of supplemental vitamin A, such as reduced growth and depigmentation, increased mortality, have been reported in other fish species (Furuita et al. 2000; Saleh, Eleraky, and Gropp 1995; Dedi et al. 1995). Similarly, Hernandez et al. (2007) observed that vitamin A in excess could have negative effects on the liver of Japanese flounder *Paralichthys olivaceus*. Both studies indicating that dietary vitamin A supplementation could potentially have toxic effects on fish performance and welfare. Increased levels of dietary vitamin A resulted in significant increase in liver vitamin A reaching 2.68 and 80 ug/g wet tissue in sunshine bass *Morone chrysops* x *M. saxatilis* whole body and liver, respectively, after receiving diet supplemented with 40,516 ug vitamin A/kg dry diet (Hemre et al. 2004). No toxic effects were reported in that study.

Certain fish species, particularly those consumed whole with the head and viscera are known to be rich in vitamin A (Roos, Islam, and Thilsted 2003; Thilsted et al. 2016). In fact, Roos et al. (2007) calculated that even small production of the vitamin A-rich fish mola *Amblypharyngodon mola* in ponds in Bangladesh can meet the annual vitamin A recommendation of 2 million children. Katsuyama and Matsuno (1988) reported that tilapia *Oreochromis niloticus*, among other species including gold fish *Carassius auratus* (Del Tito 1983) and Atlantic halibut (Moren, Naess, and Hamre 2002), able to bio-convert beta-carotene to vitamin A, suggesting possible supplementation of tilapia feeds with beta-carotene rich raw materials in order to improve vitamin A content of the fish toward human health. Hu et al. (2006) showed that tilapia was able to utilize beta-carotene to meet its dietary vitamin A requirements and the conversion ratio of beta-carotene to vitamin A was found to be 19:1 (on a weight basis). Vitamin A in fish liver can only be stored when high levels (above fish requirements) are supplemented in the feed. However, high levels of beta-carotene can become toxic to tilapia or other fish and negative effects on biological membranes and cellular signal conduction have been reported (Erdman et al. 2009). There are different foods rich in beta-carotene that could potentially become vitamin A sources for fish diets. An interest in sweet potato by-products has significantly increased in the past years mostly due to a lack of presence of wide variety of anti-nutritional substances including saponins, phytates, non-starch polysaccharides, gossypol, or phorbol esters, etc. that can negatively affect fish health by inducing intestinal inflammation. Omoregie et al. (2009) showed that dietary inclusion of sweet potato peels up to 15% did not negatively impact the fish final weights. Sweet potato inclusion, however, has been found particularly interesting for species known as ‘efficient waste foodstuff converters” due to their wide omnivorous feeding nature.

Taken together, vitamin A supplementation in fish diets could be used to increase vitamin A content in some fish species, in both whole body and/or liver, as long as the supplemented levels in feeds do not exceed fish requirements and hence, do not pose a risk of induced toxicity.

Vitamin D

Vitamin D is needed by humans for the prevention of bone disease including rickets in children and osteomalacia in adults, and has also important functions in the immune system (Roth et al. 2018). In addition, vitamin D deficiency is associated with greater risk for gestational aged births (Roth et al. 2018). Humans, particularly those living near the equator derive much of their vitamin D from exposure to sunlight, although indoor occupation, air pollution, and skin color are risk factors for deficiency. Fish is by far the most important natural dietary source of vitamin D, in some settings providing more than 90% of dietary vitamin D, although eggs, meat and mushrooms are other sources. (Nakamura et al. 2002).

In fish, vitamin D plays equally important role in skeletogenesis and ossification and hence, adequate levels of this fat-soluble vitamin should be provided in the diet particularly because the photochemical and non-photochemical biosynthesis of vitamin D unlikely occurs in fish (Mattila et al. 1999). Takeuchi et al. (1984) found that certain fish species (skipjack *Katsuwonus pelamis*, tuna *Thunnus*, cod *Gadus morhua* and pollack *P. pollachius)* contain higher levels of vitamin D in liver and other tissues compared to terrestrial vertebrates. Different levels of vitamin D have been reported within the same and across different species. For example, wild salmon has been found to have 75% higher vitamin D levels compared to farmed salmon (Lu et al. 2007) indicating among others its beneficial effect on human health. The influence of supplementation of vitamin D in fish diets seems still unclear. In sea bream *Sparus auratus*, vitamin D deficient diet contributed to hindered bone formation and growth rates as well as reduction of calcium incorporation into the skeleton (Abbink et al. 2007). Graff, Høie, et al. (2002) showed, however, that levels of this vitamin in farmed salmon can be increased by feed supplementation indicating a potential for improvement of fish muscle vitamin profile by raising fish endogenous vitamin D levels. Yet, other studies on fish indicated high levels of vitamin D causing hypervitaminosis, impaired growth, lethargy and discoloration (Halver 1989; Haga et al. 2004). In rainbow trout no correlation was observed between vitamin D levels in muscle and in the diet suggesting that saturation contents exist for vitamin D in fish flesh (Mattila et al. 1999). Whereas, a study performed by Graff, Høie, et al. (2002) showed that fish can be tolerant of high doses (up to 57 mg/kg feed) of vitamin D over a long period of time. Moreover, the study indicated that fish groups that received high vitamin D diets had significantly higher vitamin D contents in whole fish body and liver. Vitamin D is beneficial for humans but it can also positively affect fish well-being. Cerezuela et al. (2009) observed stimulation of certain immune parameters after feeding gilthead seabream with vitamin D-supplemented diets. In yellow catfish *Pelteobagrus fulvidraco* high levels of vitamin D significantly increased retention of important for humans fish whole body micronutrient content, such as sodium, potassium, phosphorus, calcium, magnesium, and zinc (Zhu et al. 2015). Furthermore, both forms of supplemented vitamin D (D_2 and D_3, plant and animal origin, respectively) were shown biologically inactive in *Labeo rohita* fish (Ashok et al. 1999). It is important to note, however, that many of the abovementioned studies testing effects of dietary vitamin D inclusion on fish performance and muscle quality were performed on fish at different ages presenting various skeletogenesis stages likely resulting in many of the discrepancies presented.

In short, vitamin D-fortified feeds seem to have potential to not only increase vitamin D content in tissues of some fish species but also enhance retention of other important micronutrients such as calcium. It is important to note, however, that differences exist between species in their inherent vitamin D levels and hence, the effect of dietary vitamin D supplementation on fish nutritional composition may vary.

Iron

Iron plays an essential role in many functions of the human body, most notably in the production of hemoglobin, which is responsible for the transportation of oxygen throughout the body (Zimmermann and Hurrell 2007). The global prevalence of anemia is about 33%, and while the relative contribution of iron vs. other nutritional and non- nutritional causes in many settings is not well understood, iron deficiency is known to be a major contributor (Kassebaum et al. 2014). Deficiency during pregnancy increases the risk of maternal mortality, during young childhood can affect cognitive development, and productivity during other life stages (Zimmermann and Hurrell 2007).

Iron is an essential nutrient also in fish. However, different fish species have different iron requirements which can change depending on dietary iron bioavailability. This may be influenced by several factors such as: chemical form, presence of other stimulating or inhibitory dietary nutrients, as well as physiological state of an animal (Andersen et al. 1997). Iron can be beneficial but might also become harmful to the animal and therefore dietary iron levels for fish must be tightly regulated to provide sufficient concentration for biological reactions without the unnecessary excess that could be harmful to the fish (i.e. oxidative stress) making it difficult to target the iron concentration that would benefit human consumer. In rainbow trout, increased levels of dietary iron caused elevation of this micronutrient in blood as well as gastrointestinal organs including liver (Carriquiriborde, Handy, and Davies 2004). Trout, however, is able to regulate elevated iron concentrations in whole body by controlling the level of iron in the blood and subsequent transfer to the liver for storage. Similarly, feeding gilthead sea bream with diets fortified with iron and other metals including zinc and copper, did not have a major effect on concentration of those minerals in tissues indicating the ability of sea bream, and possibly other fish species, to control homeostasis of these trace elements (Carpeme et al. 1999). Iron can be found in various fish tissues with highest concentration in gills, liver, kidneys, and spleen, and lowest concentration in the skin and muscle (Rajkowska and Protasowicki 2013). Whether dietary iron supplementation could be significantly increased in muscle and other edible fish parts without jeopardizing fish growth and health remains to be investigated.

Zinc

Zinc is known to play important roles in growth and immune function in humans, and zinc supplementation is recommended by the World Health Organization for the treatment of diarrhea (Keen and Gershwin 1990; World Health Organization, United Nations Childrens Fund, and VACG Task Force, 2019). Dietary zinc is equally essential for animals since the deficiency symptoms can occur within days/weeks of inadequate zinc consumption. In tilapia, supplementation of zinc resulted in higher zinc concentration in fish bones, muscle, and liver (Do Carmo E Sa et al. 2005). However, no significant differences were found in zinc levels in the latter two tissues indicating, similarly to iron, that hepatic zinc concentration is relatively constant and not affected by zinc fortification of the diet above certain fish limits. Not all zinc forms, however, can affect zinc content in fish body, including its levels in bones, which seem a suitable criterion for evaluation of zinc status with regards to fish overall health (Do Carmo E Sa et al. 2005). Huang et al. (2015) reported Zn content of the liver, muscle, bone, and scales of adult tilapia to increase with dietary zinc levels from 15.9 to 53.5 mg/kg over a 12-week period suggesting a possibility for targeting zinc levels in the edible parts of tilapia toward enhancement of human health. However, as in the case of iron, more studies are needed to assess if zinc supplementation in fish diets is truly possible to augment the levels of this micronutrient in different fish species to meet consumers' nutritional requirement for zinc.

Calcium

Calcium is essential in humans for bone health and in pregnancy, calcium supplementation to deficient populations can help prevent pre-eclampsia, a major cause of maternal mortality (Imdad, Jabeen, and Bhutta 2011). Fish eaten as whole, such as mola, are considered a good source of calcium. In fact, it has been shown in mammals that absorption of calcium from small fish bones was as efficient as absorption from skimmed milk (Larsen et al. 2000). Malde, Bügel, et al. (2010) found that salmon bone meal is characterized by presence of highly available calcium and hence, could also serve as a good and natural calcium source in food and feeds for humans and animals, respectively. Calcium is mostly accumulated in fish bones but as much as 24% can also be stored in scales (Shiau and Tseng 2007). If the water is rich in calcium fish can absorb calcium from their surrounding environment to achieve, to some extent, its calcium requirements. Otherwise, calcium must be obtained from the feed. O'Connell and Gatlin (1994) showed that blue tilapia *Oreochromis aureus* weight gains and calcium levels were significantly increased in scales and bones in groups that received calcium supplemented diets compared to calcium-deficient feeds irrespective of vitamin D supplementation in low-calcium water. Khajepour and Hosseini (2012) study indicated that addition of 2–3% of citric acid in Beluga *Huso huso* diet increased calcium contents of serum and muscle and the authors urged to investigate further the effects of organic acids on mineral composition of fish muscle. In juvenile grass carp *Ctenopharygnodon idella*, the dietary calcium required for optimal growth performance and maximum tissue concentration was estimated as 10.4 g/kg. In juvenile tilapia, the highest calcium concentration in bones was reported in fish fed diets supplemented with or above 4.7 g/kg. Nevertheless, a negative excess of calcium supplement has also been reported in grouper *Epinephelus coioides* (Ye et al. 2006). Calcium requirement in fish might change with a higher or lower presence of other dietary nutrients, such as phosphorus, which can affect fish whole body calcium contents (Liang et al. 2012). Dietary magnesium, however, had no effect on calcium status in scales or bones (Ye et al. 2009). Interestingly, phytic acid present in plant raw materials has also been linked to low whole-body concentration of calcium and other minerals in salmon (Helland et al. 2006). There is also extensive literature available on the interaction effects between calcium and heavy metals and reader is referred to the appropriate literature (Berntssen et al. 2003; Baldisserotto et al. 2004; Baldisserotto, Chowdhury, and Wood 2005; Baldisserotto, Chowdhury, and Wood 2006; Alves and Wood 2006; Abdel-Tawwab et al. 2007; Klinck and Wood 2013).

Dietary calcium supplementation might be possible in aquaculture species to increase its calcium content in fish edible parts, such as muscle, though presence of other micronutrients in the diet and fish species must be considered.

Selenium

Selenium is an essential trace element in human and animal nutrition. Selenium plays role as an antioxidant and catalyst for the production of thyroid hormone, stimulates functioning of the immune system, and acts as an antioxidant in cardiovascular disease and cancer prevention (Molnár et al. 2012; Rayman 2000). According to U.S Department of Health and Human Services, the recommended dietary allowance for humans is 15–55 μg/day depending on age, gender, and health status. Selenium functions primarily in a form of selenoproteins and its role can be structural and enzymatic. The bioavailability of selenium, which is the concentration of nutrient absorbed and utilized by an organism to contribute to the required physiological function, varies considerably between different food types. For example, Ørnsrud and Lorentzen (2002) showed that bioavailability of selenium in rats was higher after feeding selenomethionine-enriched salmon fillets-based diet compared to selenite supplemented feed.

In fish, such as yellowtail kingfish *Seriola lalandi*, supplementation of fishmeal-based feeds with selenium in a form of selenocystine, selenomethionine, or commercial selenium supplement, resulted in increased muscle selenium concentration of 0.35, 0.61, and 0.62 mg/kg, respectively, compared to selenite which had no effect on the muscle selenium levels (0.24 compared to 0.21 mg/kg selenium in muscle in basal-selenium deficient group) (Le and Fotedar 2014). Simultaneously, dietary selenium levels between 15 and 21 mg/kg were indicated as a threshold level for juvenile yellowtail kingfish to prevent reduced feed intake, growth and any pathological changes in fish tissues (Le and Fotedar

2014). Molnár et al. (2012) found that although no differences were found in the growth of Nile tilapia *niloticus*, significant increase in selenium content in muscle fillets was detected when fish received elevated selenium levels in the diet. In addition, the maximum selenium concentration in muscle was achieved with 2 mg/kg (actual content 2.47 mg/kg) dietary supplementation resulting in 128 µg/kg Se in fillets after 6 weeks of feeding. Moreover, the effect of diet fortification with selenium on fish muscle has been shown in various species including: Atlantic salmon *salar* (Lorentzen, Maage, and Julshamn 1994), rainbow trout *Oncorhynchus mykiss* (Hilton, Hodson, and Slinger 1982), coho salmon, *Oncorhynchus kisutch* (Felton et al. 1996), and channel catfish *Ictalurus punctatus* (Gatlin and Wilson 1984). In African catfish *Clarias gariepinus* supplementation of garlic containing high concentration of selenomethylselenocysteine and γ-glutamyl-seleno-methyl-selenocysteine (8.5 mg/kg total Se), known to have anti-carcinogenic properties, resulted in total concentration of selenium in the fillet of 0.9 mg/kg (Schram et al. 2008) indicating significant variation in fish in the utilization (bioavailability) of different sources of selenium. The same authors later found total selenium level in the African catfish fillet to reach 0.7 mg/kg after feeding diets with selenium level of 11.7 mg/kg after 10 days of feeding right before harvest (Schram et al. 2009). In that study, similarly, dietary selenium fortification was achieved by inclusion of selenium-enriched garlic supplied as a dry powder in the feed. Furthermore, Zhou et al. (2009) indicated that selenium in the form of nanoparticle or selenomethionine not only increased selenium concentration in muscle of crucian carp *Carassius auratus gibelio* but also improved the growth of the fish.

In short, feed fortification with selenium seems to increase the level of this mineral in fish flesh in a relatively short period of time although the outcomes might differ depending on selenium bioavailability and hence its chemical form and/or source.

Omega-3 polyunsaturated fatty acids

Omega-3 PUFA are critical in human diet. The most universally available PUFA n-3 is ALA derived from dietary oils from plant and animal sources. The main health benefits, however, have been assigned to the marine forms of the long-chain n-3: DHA and EPA obtained mainly from fish but also from seafood and algae (Ellulu et al. 2015). Since the conversion of ALA to EPA and DHA in humans is not efficient, consumption of foods rich in these essential fatty acids is recommended (Ganesan, Brothersen, and McMahon 2014). There is evidence linking consumption of n-3 PUFA with many human health benefits. PUFA are incorporated in biological membranes and hence, affect their viscosity, but they also play an important role in anti-inflammatory processes (Calder 2015). Both EPA and DHA are essential for proper fetal development and seem to be beneficial in the prevention or treatment of several diseases (Swanson, Block, and Mousa 2012). The consumption of n-3 PUFA has been related to reduction of cardiac disease and risk of stroke. Approximately 140–600 mg per day of n-3 PUFA DHA and EPA is recommended for daily consumption for humans (Bruneel et al. 2013; Ganesan, Brothersen, and McMahon 2014). The intake of up to 3 g/day of marine omega-3 fatty acids has been governed as 'Generally Recognized As Safe' for inclusion in human diet (Kris-Etherton, Harris, and Appel 2002). An optimal balance/ratio of n-6 to n-3 PUFA has also been recommended and its alterations have been associated with health risks including cardiovascular disease, cancer, and diabetes. In modern diets, n-6 PUFA are more common, therefore focus has been placed on proper levels of n-3 PUFA necessary for human health. Sprague et al. (2017) clearly demonstrated a variation in EPA and DHA levels in seafood products available to consumers and suggested that weekly intake of salmon or trout should be nearly two times higher compared to intake of mackerel in order to meet the recommended weekly requirement for both EPA and DHA. Currently, many supplements and food products fortified with n-3 PUFA are available on the market. In general, it has been suggested that the daily intake of n-3 PUFA can be increased using nutriceuticals such as encapsulated fish oil capsules, functional food, which are products enriched with n-3 PUFA, and whole foods, such as fish (Patterson and Stark 2008). The bioavailability of n-3 PUFA from fortified foods is similar to pharmaceutical/nutritional supplements (Kolanowski 2005). However, human absorption of n-3 PUFA from food products has been reported to occur at faster rates compared to supplements (McManus, Merga, and Newton 2011).

Fatty acid profile of fish muscle can be manipulated by modifying fatty acid composition of fish diet (Sprague, Dick, and Tocher 2016) and hence, it is common that farmed fish usually have lower percentages of n-3 PUFA compared to fish in the wild. This is caused largely by substitution of dietary fish oil mainly produced from marine species (i.e. herring, sardine, sand, eel, anchovy, cod, krill) with vegetable oil in the diets for aquaculture species rendering the nutritional quality of fish meat. Consequently, alternative raw materials and additives are being identified for inclusion in fish feeds to optimize fish fatty acid profile contributing to health benefits associated with consumption of fortified fish products (Bourre 2005). Tocopherol (vitamin E) is a known antioxidant which prevents fatty acid oxidation in cell membranes and a speculation exist that vitamin E and n-3 PUFA levels are tightly related in tissues. Indeed, Navarro et al. (2012) observed that tilapia fed diets supplemented with vitamin E (100–150mg/kg diet) had improved n-3 to n-6 ratio as well as high level of PUFA in muscle tissue. There have also been attempts to engineer certain crops to accumulate high levels of EPA and/or DHA in its seed oil. Genetically engineered Camelina has been reported to be a source of n-3 PUFA and thus, provide high levels of these fatty acids in farmed fish fed reduced fish oil diets without impairing their nutritional quality (Betancor et al. 2015). Moreover, genetically modified crops have now also been proven to produce the n-3 PUFA in the field using common agricultural practices (Usher et al. 2015).

Nevertheless, whether production of such crops is scalable remains uncertain. Chen et al. (2006) indicated that inclusion of 15% of flaxseed oil in rainbow trout diet improved the levels of omega-3 fatty acids in trout fillets. However, the authors also showed that although the supplementation of flaxseed oil at 15.0% or 8.5% inclusion level increased concentration of linolenic acid in fish fillets, the EPA and DHA contents decreased. Dos Santos et al. (2014) found that inclusion of perilla *frutescens* seed bran in Nile tilapia diet significantly affected the fatty acid composition of tilapia muscle at inclusion level of 384% contributing to increase in omega-3 PUFA and hence, positively affected tilapia muscle nutritional quality. Perilla is a plant found in Asia commonly used in gastronomy and traditional medicine. Perilla has many anti-inflammatory, anti-carcinogenic, and anti-bacterial properties and the seeds are rich in oils (35-45%) with high concentrations of PUFA. Replacement of sunflower oil with perilla oil in tilapia diets improved the n-3 fatty acid profile, particularly with respect to ALA and DHA in tilapia fillets (Carbonera et al. 2014). Trattner et al. (2008) found that dietary sesamin (component of sesame oil) supplementation can increase white muscle DHA concentration in rainbow trout in vegetable oil-based diets.

The nutritional composition of algae gives it a potential for becoming sustainable source to substitute the conventional ingredients (fish oil) in aquaculture feeds. Besides the n-3 PUFA, algae also contain nutritionally important components such as carotenoids and have antioxidant properties that stabilize PUFA and consequently enhance lipid stability (Bruneel et al. 2013). Norambuena et al. (2015) found that Atlantic salmon n-3 PUFA levels in whole body increased after receiving diets with inclusion of algae (*Ulva ohnoi* or *Entomoneis* spp.). However, authors argued that this increase was still marginal meaning that inclusion of algae to replace fish oil would not necessarily be feasible. It has been observed in the same species, that inclusion of seaweed led to increase of up to 30 and 60% in concentrations of EPA and DHA, respectively (Wilke et al. 2015). Ragaza et al. (2015) conducted a feeding trial with inclusion of red seaweed *Eucheuma denticulatum* in feeds for Japanese flounder *Paralichthys olivaceus* and found increased concentration of n-3 PUFA in dorsal muscle compared to fish fed fish meal and soy protein concentrate-based diets making it a viable dietary ingredient that could potentially enhance the fatty acid profile of fish flesh.

Fish muscle omega-3 fatty acid profile can be enhanced and optimized to meet human requirements for essential fatty acids even through feeding of the fish with fish oil-deprived formulations. However, how the alternative omega-3 sources such as algae or genetically engineered crops will influence the cost of feeds and the fortified fish product, and hence its availability particularly in low- and medium-income countries remains uncertain.

Discussion

Beveridge et al. (2013) argued that it is not fish availability that is necessarily a concern but rather fish nutritional profile and the nutrients that fish provide, which are significantly influenced by how the animal is fed. It is well-known that nutrient composition of many farmed fish is different compared to fish in the wild. This tendency becomes more apparent with constant intensification of aquaculture production methods involving increasing dependence on commercial formulated feeds. The literature regarding fortification of fish feeds with nutrients essential for humans is scarce. Most of the studies we identified in this review evaluated supplementation effects on fish growth and health performance and welfare focusing predominantly on responses in fish whole body, liver, and bones and marginally on the muscle tissue. It may therefore be important to consider the effects of dietary supplementation on the nutrient content of fish edible parts. In the US and Europe those edible portions would most certainly be fish white muscle which seems wasteful compared to the scope of all the tissues available in fish body. Globally approximately 1.3 billion ton per year of the edible parts of food produced for human consumption gets wasted which is nearly 30% of the total edible portion of the food produced. This is particularly prevalent in the developed world. In Europe and North America for example, 95–115 kg of food per year per capita is wasted (food frequently being thrown away even if it is still suitable for consumption) compared to only 6–11 kg per year in sub-Saharan Africa and South/Southeast Asia (FAO 2011). This suggests that while improving and increasing current food production systems is of paramount importance, more solutions should also be proposed to better utilize by-products across the food supply chain and reduce the waste volumes particularly on a consumer household level.

While only the flesh and occasionally the skin or heads of larger fishes tend to be consumed, small fish are often eaten as whole. The micronutrient content of small fish is known to be high but it is mostly concentrated in the bones, heads and gut, and hence, these fish must be eaten whole to provide full nutritional spectrum (Thilsted 2012). This does not necessarily exclude the possibility of consuming other tissues from larger fish. In fact, Abdi (2014) suggested that liver of certain fish species is a valuable source of protein and lipid with excellent amounts of omega-3 including EPA/DHA, and omega-6, and therefore, liver ought to be utilized for human consumption. Fish liver has traditionally been the most important vitamin D source for the coastal population of Northern Norway during the winter months since at these latitudes the sun-stimulated vitamin D production declines during a considerable part of the year (Brustad et al. 2004).

Fish bones are widely available and are an important raw material due to the high calcium content that can conveniently be used as a high-quality food ingredient or supplement (Malde, Bügel, et al. 2010). Indeed, Malde, Bügel, et al. (2010) showed that enzymatically treated bones of Atlantic salmon and Atlantic cod are well absorbed sources of calcium in young men. Nevertheless, limited studies have been carried out to evaluate bioavailability of fish bone calcium in humans (Hansen et al. 1998; Larsen et al. 2000). Fish bone material has potential to become fortified food converted into an edible form by various methods which allow for softening its structure (Kim and Mendis 2006).

Much of the work on fish as functional food has been concentrated on inclusion of omega-3 fatty acids for highly demanded consumers. The consumption of n-3 PUFA enriched foods is critical especially in populations where consumption of meat, muscle, and seafood is very low. These essential polyunsaturated fatty acids can be obtained from different sources ranging from capsule supplements to fortified dairy, egg, or meat products. Harris et al. (2007) found that the content of EPA and DHA in the blood was not different in individuals who consumed fish or fish oil capsules for four months. It is important to note though that nutritional benefits of fish consumption relate not only to the omega-3 content but also the utilization of proteins of much higher biological value compared to other animal proteins, higher levels of taurine linked to reduction of cardiovascular risks, as well as certain trace elements including selenium, calcium, vitamin D and B complex vitamins (He 2009). McManus, Merga, and Newton (2011) suggested the 'whole food' approach to be most feasible since the nature of the food matrix can greatly influence the utilization of certain nutrients. He (2009) concluded that the health-promoting effects of fish consumption on the risk of cardiovascular disease most likely result from the synergistic interaction between nutrients in fish and therefore it is likely that consumption of whole fish would have much greater impact on human health compared to fish oil supplement.

Fish most certainly extend beyond being a protein source and they can serve as an ideal vector for delivery of many vital nutrients. The fortification of fish diets particularly with vitamins and minerals, however, has not been directed toward human health but rather toward improvement of fish growth and/or health performance. Thus, future research should focus on enrichment of fish feed to develop a fish product with enhanced properties that would contribute to improved nutritional security and disease prevention particularly for people in developing countries, most vulnerable to nutritional deficiencies.

Conclusions

1. Contrary to common perception, farmed fish is increasingly important source of fish for poor populations, especially in Asia (Toufique and Belton 2014; Belton, Bush, and Little 2018). If replacing wild caught fish, it is important to consider the nutrient content of farmed fish from the standpoint of human nutrition.
2. Many studies have been done to identify the nutrient requirements needed to maximize the health and growth of fish. Virtually no studies have been done to directly assess human health benefits of enhancing the nutritional content of fish through feeds.
3. Most studies have been completed in species that are commonly consumed in high income countries (salmon etc.). More studies exploring the impact of feed on nutrient composition of fish consumed by poorer populations are needed, especially using locally available ingredients.

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