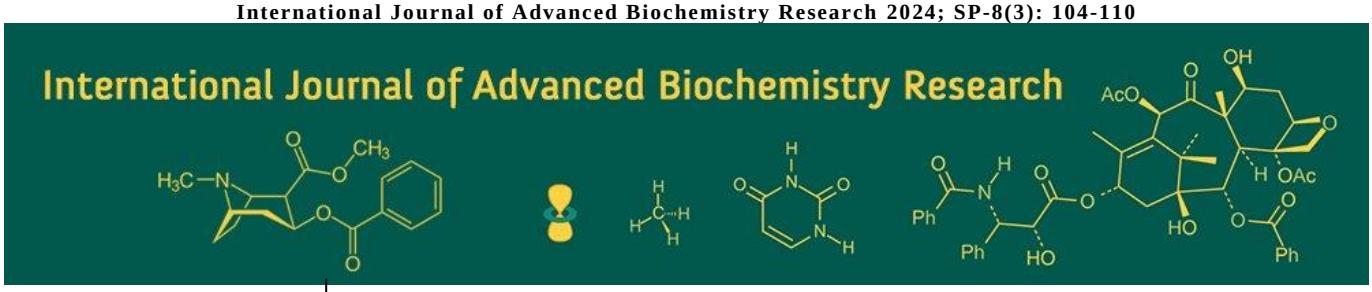

ISSN Print: 2617-4693
ISSN Online: 2617-4707
IJABR 2024; SP-8(3): 104-110
www.biochemjournal.com
Received: 02-12-2023
Accepted: 09-01-2024

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Strategic nutraceutical approaches for enhancing fisheries and aquaculture: A comprehensive review

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DOI: https://doi.org/10.33545/26174693.2024.v8.i3Sb.701

Abstract
Nutraceuticals are bioactive compounds or substances that have potential health benefits when administered as part of the diet in animals, including fish and other aquatic organisms. In fisheries and aquaculture, nutraceuticals are used to improve the cultured species' growth, health, and overall performance. In addition to their health benefits, nutraceuticals from fisheries and aquaculture can also be used in aquaculture to improve the growth and health of fish. For example, omega-3 fatty acids can be added to fish feed to improve the fatty acid composition of the fish flesh. This can make the fish more appealing to consumers and have health benefits for the people who eat the fish. They can help to improve cognitive function and memory. Nutraceuticals help to boost the immune system and fight off infection. The use of nutraceuticals in aquaculture is a growing field. As more research is conducted on these compounds' health benefits, their use will likely become more widespread.

Keywords: Nutraceuticals, probiotics, Health management, herbal extracts, fatty acids

Introduction
The conceptualization of the interrelation between the utilization of appropriate comestibles for the promotion of health and therapeutic advantages dates back to approximately 2500 years ago when Hippocrates first postulated these concepts. Nonetheless, the nomenclature "nutraceuticals" was officially coined by Dr. Stephen D. Felice in 1989, as he defined it as "a comestible or alimentary product that elicits health-promoting and medicinal effects, encompassing the realms of disease prevention and treatment" (Kalra, 2003) [28]. Entire, nutrient-dense comestibles such as Spirulina, garlic, or specific bioactive compounds like vitamins, lycopene, or omega-3 fatty acids possess the attributes of a nutraceutical. It often proves to be a challenging endeavor to differentiate between the designations of food, nutraceuticals, dietary supplements, functional foods, and pharmaceutical agents (Gupta *et al*., 2010) [18].

In accordance with Zeisel (1999) [53], nutraceuticals are distinct from dietary supplements, as they are typically integrated into the regular dietary intake and contain one or more bioactive components that exhibit physiological effects and possess the potential to enhance health, all within the natural food matrix. Their perceived safety and the promise of nutritional and therapeutic advantages have propelled nutraceuticals to greater popularity compared to pharmaceutical drugs and conventional dietary supplements. While the original concept was primarily established for the enhancement of human health, in recent times, it has also gained significant recognition in the realm of animal nutrition.

Nutraceuticals represent food products originating from both terrestrial and marine sources that hold significance for healthcare purposes. The term "nutraceuticals" encompasses a diverse array of products derived from natural sources, including isolated nutrients, dietary supplements, genetically engineered designer foods, herbal products, processed foods, and beverages.

A nutraceutical is a label employed to characterize any product sourced from food materials that offers supplementary health benefits beyond the fundamental nutritional content present in typical foods. In simpler terms, a nutraceutical, occasionally referred to as a "bioceutical," serves as a pharmaceutical alternative, purporting to provide physiological advantages for organisms.

These constituents of nutraceuticals are not recognized as essential nutrients but are acknowledged as bioactive substances possessing one or more health-enhancing properties.

Types of Nutraceuticals

Based on the bio-functional properties of bioactive compounds from terrestrial and marine sources are classified into the following.

1. **Dietary Supplements:** As per the definition provided by the Food and Drug Administration (FDA) in the USA in 1995, dietary supplements are characterized as products composed of "dietary constituents that are orally ingested to supplement the nutritional needs of the diet." The term "dietary constituents" primarily pertains to bioactive elements encompassing amino acids, vitamins, minerals, fibers, crucial metabolites, and specific enzymes. These dietary supplements may also encompass concentrated extracts made available in various forms, including tablets, capsules, powders, liquids, or any other dosage form (Priyadarshani & Rath, 2012) [35].
2. **Functional Food:** Functional foods are food products that are naturally abundant in nutrients and can also be fortified with essential nutrients, as noted by Jones and Jew in 2007. In accordance with Health Canada, functional foods are described as regular foods containing specific ingredients with therapeutic effects and nutritional value, as indicated by Jalili *et al*. in 2001 [23].

In Japan, the definition of functional foods is based on three key criteria

- Functional foods must be derived from natural sources and consumed in their unaltered, native state, as opposed to being processed into different dosage forms such as tablets, capsules, or powders.
- They should be consumed as a regular part of the daily diet.
- Functional foods should serve a dual role in preventing and managing disease while contributing to essential biological processes, as stipulated by Arai in 1996.

Medicinal food

Medical foods are uniquely formulated products designed to be consumed under the guidance and supervision of a physician. They are specifically intended for the dietary management of particular diseases that have well-defined nutritional requirements which cannot be adequately addressed through a regular di*et al*one. This sets medical foods apart from dietary supplements and functional foods, as these two categories do not meet the stringent criteria and requirements associated with medical foods, as highlighted by Radhika *et al*. in 2011 [36].

Role of nutraceuticals in aquaculture

The application of nutraceuticals has garnered significant attention in the aquaculture industry due to their potential to enhance production performance, promote growth, boost immunity, and improve feed utilization, as supported by studies such as Sinha *et al*. in 2007 [41] and Tejpal *et al*. in 2021 [47, 48]. A wide range of nutraceuticals are being employed in aquafeed formulations and on aquaculture farms, encompassing various categories such as enzymes, methyl donors, nucleotides, Levans, immunostimulants like chitin, chitosan, polychaete and tunicates extracts, vitamins, antioxidant minerals, amino acids, anabolic growth promoters, organic acids, carotenoids, and more.

It is evident that the utilization of nutraceuticals in the aquafeed industry has a favorable impact on feed utilization, immunity, flesh quality, stress tolerance, reproductive and productive performance, and the overall water quality in aquaculture settings. This is largely attributed to reduced feed wastage and improved feed efficiency. The stagnation in marine production coupled with heightened consumer demand has placed substantial pressure on the aquaculture sector to increase its output. The limitations of available land and water resources have led to more intensive inland culture systems, which, in turn, are susceptible to disease outbreaks due to suppressed fish immunity caused by stress. The aquatic environment is host to numerous potential pathogens waiting for opportunities to infect fish. Recent years have witnessed several disease outbreaks in aquaculture farms. To combat such challenges, the use of antibiotics and drugs has become a common practice. However, the indiscriminate use of these chemicals has led to issues like antibiotic resistance, residue accumulation in aquatic ecosystems, and other adverse effects. In this context, the adoption of nutraceuticals as an alternative to conventional drugs and chemicals presents an ideal approach to address these concerns. Research findings suggest that nutraceuticals possess immune-boosting and growth-enhancing capabilities in fish. They have been shown to increase feed intake, enhance the anti-stress and antimicrobial abilities of fish and shellfish, and induce maturation without causing detrimental effects. Some feed additives in aquaculture are also categorized as nutraceuticals, as observed in the work of Brower in 1998.

Stress in aquatic systems is caused due to several factors. The high stocking density, variation in climatic conditions, exposure to pesticide or insecticide, malnutrition, and use of plant-based ingredients containing anti-nutritional factors can cause stress to fish. Today, researchers are come up with several compounds that can mitigate the effect of stress in fish. The classification of these compounds can be done according to their function and chemical nature. The commonly used nutraceuticals in aquaculture can be classified as

Traditional: Ancient civilizations such as those in India, China, Egypt, and Sumer were profoundly aware of the significance of food as a form of medicine, and this knowledge was documented in their epics and other historical texts. For instance, in ancient Indian medical science, Ayurveda, the pivotal role of food for therapeutic purposes was clearly emphasized. Traditional, simple, and naturally occurring foods that were traditionally employed for their health benefits are categorized as "traditional nutraceuticals." On the other hand, products that have been commercially enhanced with additional nutrients or that have been developed using modern technologies like breeding and hybridization to increase their specific nutritional content are classified as "nontraditional nutraceuticals." This recognition of the medicinal potential of food in ancient civilizations serves as a historical testament to the long-standing understanding of the profound connection between nutrition and health, a concept that continues to evolve and gain importance in contemporary times.

Based on the chemical nature

i) Amino acids and peptides

Ancient civilizations such as those in India, China, Egypt, and Sumer were profoundly aware of the significance of food as a form of medicine, and this knowledge was documented in their epics and other historical texts. For instance, in ancient Indian medical science, Ayurveda, the pivotal role of food for therapeutic purposes was clearly emphasized. Traditional, simple, and naturally occurring foods that were traditionally employed for their health benefits are categorized as "traditional nutraceuticals." On the other hand, products that have been commercially enhanced with additional nutrients or that have been developed using modern technologies like breeding and hybridization to increase their specific nutritional content are classified as "nontraditional nutraceuticals." This recognition of the medicinal potential of food in ancient civilizations serves as a historical testament to the long-standing understanding of the profound connection between nutrition and health, a concept that continues to evolve and gain importance in contemporary times.

ii) Fatty acids

Polyunsaturated fatty acids (PUFA) belong to the n-3 and n-6 family and are precursors of biologically active eicosanoids (Bakhle, 1983) [5] and are essential for inflammatory responses in fish. (JOLLY, 1999) [26] showed n3 PUFA increased immunity in rohu fingerlings. There is a report that the dietary inclusion of 3% PUFA causes immune-suppression in juveniles (Fontana *et al*., 1999) [15].

iii) Nucleotides

The dietary nucleotide inclusion in fish enhances the immunity (Beale *et al*., 1999; Snyderman *et al*., 1999) [7, 42] A study in salmon showed that the overall health of the fish was improved by the dietary nucleotide supplementation (JOLLY, 1999) [26] (Sukumar *et al*., 1999) [45]. Moreover, (Pepin *et al*., 1999) [33] reported that dietary RNA improved survival in fish. (Jha *et al*., 2007) [25] reported that 0.8% inclusion of nucleotide can enhance the immune response in catla fingerlings.

iv) Vitamins

Vitamins are micronutrients which are essentially required in smaller quantity to perform vital functions of the animal. Vitamins like A, C and E are important antioxidants, which enhance the immunity in fish. High levels (3000mg/kg diet) of ascorbic acid enhance the antibody production and complementary activity (Soliman, 1985) [43]. According to (Chen *et al*., 2004) [10] the dietary inclusion of more than 100mg/Kg vitamin C showed an enhanced immune protection in fish. Vitamin E supplementation reduced nitrite stress in rohu (Ciji *et al*., 2012) [12] and showed immune-boosting activity in channel catfish (Zhu *et al*., 2012) [55]. Vitamin A and beta carotenes are strong antioxidants in biological system and the supplementation of astaxanthin showed an immunomodulatory effect in rainbow trout (Thompson *et al*., 1995) [50]. Pyridoxine or Vitamin B6 is reported to have anti-stress effect because it can boost the production of serotonin and GABA. A dose standardization study in our lab reported that the dietary supplementation of pyridoxine at 100mg/Kg diet is optimum for stress reduction and growth enhancement (Akhtar *et al*., 2013) [3]. Similarly, Pantothenic acid can down regulate the hyper-secretion of cortisol and hence a control in stress.

v) Minerals

Minerals are the inorganic nutrients which can also act as anti-stress agents. The supplementation of minerals in both organic and inorganic forms is found to be effective for stress mitigation in fish. Supplementation of zinc picolinate decreased the oxidative stress in rainbow trout (Kucukbay *et al*., 2006) [29]. Dietary selenium in organic forms also reduced oxidative stress in groupers (Rider *et al*., 2009) [37].

vi) Polysaccharides

Polysaccharides are primarily utilized to target the non-specific immune system of aquatic animals. In recent years, a wide range of polysaccharides have been employed as immunostimulants in aquaculture, including microbial levan, beta-glucan, chitin, lactoferrin, inulin, and more. One notable example is β-glucan, which consists of glucose polymers with a backbone of β-(1-3) linked β-D-glucopyranosyl units. β-glucans are known to interact with a variety of cellular receptors, allowing them to activate these receptors. This activation has been associated with enhanced resistance against bacterial and viral infections in fish, as demonstrated in the study by Zhang *et al*. in 2014 [54]. These polysaccharides, by stimulating the non-specific immune responses in aquatic animals, contribute to bolstering their ability to combat various pathogens and infections, thereby promoting overall health in aquaculture settings.

vii) Herbal extracts

Herbal extracts contain bioactive compounds capable of scavenging reactive oxygen species and bolstering the immune system in animals. Several plant extracts have demonstrated their ability to boost immunity and mitigate stress in fish, as documented in studies by Harikrishnan *et al*. in 2011 [19] and Serradell *et al*. in 2020 [40].

Certain bioactive compounds, like Rutin found in Toona sinensis, are potent antioxidants and anti-stress flavonoids. These compounds have been reported to be effective in promoting the health of crustaceans. Research conducted has shown promising results with guava and mango leaf extracts. Specifically, the inclusion of 0.5% guava and/or mango leaf extract in the diet was found to enhance immunity in *Labeo rohita* fingerlings, as described in the study by Fawole *et al*. in 2016 [14]. Additionally, another study demonstrated that feeding ethanolic leaf extract of *Moringa oleifera* at 0.25% in the diet for 20 consecutive days led to enhanced immunity in Nile tilapia, as reported by Tekle and Sahu in 2015. These findings highlight the potential of herbal extracts to positively impact the immune system and stress resilience in fish.

3. Based on the functions

i) Anti-stress and antioxidant nutraceuticals

Most of the vitamins, minerals and herbal extracts fall under this category.

Dietary supplementation of bovine lactoferrin at a dose of 1200mg/kg diet showed a reduction in salinity stress in groupers (Saichiro *et al*., 2006) [38]. The herbs, Astragalus membranaceus and Astragalus paniculata are found to be effective antistress agent in Cyprinus carpio and tilapia (Wu *et al*., 2007) [52].

ii) Immunostimulants

The immune system of fish and shell fish are not very well developed like terrestrial animals and the major target in many cases are the non-specific immune system. Many of the polysaccharides and the oligosaccharides enhance the non-specific immune system in fish and shellfish. The studies show that feeding 5mg/kg levamisole in carp diet enhanced the phagocytic activity. (Boonyaratpalin and New, 1995) [8] showed a high dissolved oxygen tolerance and immune stimulation in black tiger shrimp when fed with peptidoglycan. Beta glucan also showed enhanced resistance to bacterial and viral infections in crustacean (Misra *et al*., 2006) [32]. Microbial Levan at 1% concentration enhanced the immunological parameters in rohu fingerlings and similarly, the inulin also enhances the immune response in fish. A number of plant materials like saponin, tannin, glycyrrhizin, azadirachtin etc are also found to be immune enhancers in fish and shell fish.

iii) Antimicrobial and viral nutraceuticals

Sulfur-containing nutraceuticals such as onion, garlic, thioles, and sulphides, terpene-based compounds found in oregano, turmeric, and ginger, phenolic compounds like cloves, nutmeg, cinnamic acid, and tannin, glycosides such as sugar, aldehydes like citral and citronellol, as well as esters and alcohols, are known to possess antimicrobial properties. These compounds have the potential to inhibit the growth of microorganisms, making them valuable in various applications, including aquaculture. In aquaculture, many of these antimicrobial agents are still in the experimental stage, but they hold promise for controlling and preventing microbial infections in aquatic animals. Additionally, several plant extracts and immunostimulants like glucan, chitin, lactoferrin, and levamisole also exhibit antimicrobial and antiviral properties. This dual functionality makes them valuable in enhancing the health and disease resistance of fish and other aquatic organisms, which is particularly important in the context of aquaculture.

iv) Growth promoters

There are various natural compounds and micronutrients showing growth enhancing property in fish. The inclusion of spirulina has found to have growth promotive effect in tilapia, (Abdel-Tawwab *et al*., 2008) [1]. Spirulina is rich in carotenoids and phenolic compounds and dietary supplementation of it enhanced the growth and phosphatase activity in rohu exposed to metallic stress (James, 2010) [24]. Yeast and seaweed extracts are also a found to be growth and immune booster in fish. The herbal growth promoters are found to be supporting the transcription rate to promote growth. Enrichment of artemia nauplii with herbal products like stressol I and stressol II were found to be growth promoting in Penaeus indicus (Chitra, 1995) [11]. According to (Francis *et al*., 2005) [17] the inclusion of quillaja saponins enhances the metabolic rate and overall growth in tilapia.

v) Acidifiers

Organic acids in isolation or in combination can improve the digestion, intestinal micro flora and intestinal health status which are commonly called as acidifiers. Additions of acidifiers in feed improves the shelf life of the feed, support digestion by providing suitable pH for enzyme action and even act as intermediates in TCA cycle. A study from our lab showed that the application of citric acid (3%) along with exogenous phytase enhance the action of phytase and promote mineral availability in rohu (Baruah *et al*., 2007) [6]. Formic acid and acetic acid are other important acidifier studied in animal diets.

vi) Prebiotics, probiotics and symbiotic

Probiotics can be defined as "a viable mono or mixed culture of microorganism which, when applied to and animals or man beneficially affects the host by improving the properties of indigenous flora" (Havenaar, 1992) [20] while prebiotics are the non-digestible food ingredients which promote the growth and colony formation of gut microflora. When both prebiotics and probiotics together supplied to the system it has synergistic effect and is called as synbiotics. The probitotics suppresses the bacterial pathogens, and helps in production of special metabolites, which enhance the immune system. The most commonly used probiotic organisms in aquaculture are Lactobacillus sp., Enterococcus spp, Bifidobacterium spp, Bacillus sp. and Streptococcus spp. The major prebiotics studied in aquaculture systems include Mannan oligosaccharides (MOS), Xylan oligosaccharides (XOS), Fructan oligosaccharides (FOS) etc., which supports the establishment of favourable microbes, helps in absorption of nutrients and immune modulation of species.

Reports on utilization of MOS in fish showed that the survival, immunity and growth were improved in rainbow trout (Staykov *et al*., 2007) [44], channel catfish (Welker *et al*., 2007) [51] and common carp (Staykov *et al*., 2007) [44].

vii) Nutrizymes/exogenous enzymes

The exogenous enzymes which act as nutraceuticals are called as nutrizymes and it supports in enhancing the digestibility of feed and enhance the growth. Plant based feed ingredients naturally contains antinutritional factors and cellulose in it. This creates digestive imbalances in fish and has to be supported by external enzymes to reduce the negative effects. The digestive enzymes like lipase, cellulase, protease, glucanase, phytase and microbial amylase enhance the digestion in fish fed with plant-based ingredients.

Studies have shown that glucanase increases the protein digestibility in soybeans from 74-95% and the phytase improves the availability of minerals and protein, which makes complex with makes complex with phytic acid (Coon, 1998). The exogenous chitinase helps to improve the digestion of chitin containing ingredients in the diet. Addition of exogenous carbohydrase improves the utilization of carbohydrate in carnivorous fishes. In a study conducted in our lab we could onserve that Non – gelatinised corn supplemented with microbial α – amylase at suboptimal protein in the diet of L. rohita fingerlings enhanced the growth and cell size (Kumar *et al*., 2014) [30].

Mode of delivery

Nutraceuticals can be delivered in different modes like parental, directly oral administration and dietary supplementation. In a study on nucleotide showed that the yeast RNA supplementation in oral mode enhanced the phagocytic activity in common carp (Sakai *et al*., 2001) [39], while high dietary RNA supplementation affected the growth and protein accretion European seabass (Peres and Oliva-Teles, 1999) [34]. Injection of chitin showed an enhanced immune system in fish. But most of the studies

indicate that the supplementation through diet in a protected way is more economical and efficient. Nano delivery of nutraceuticals is a field yet to be studied in detail. Nano zinc supplementation studies were conducted in our lab and found to be effective in enhancing growth and immunity compared to nascent inorganic zinc supplementation. The targeted tissue delivery, prevention of loss of micronutrients and reduction in cost are added advantages of Nano delivery systems.

Future scope

Recent years have seen a surge in disease outbreaks affecting shrimp and fish farms worldwide, resulting in significant crop losses, with White Spot Syndrome Virus (WSSV) and Early Mortality Syndrome (EMS) among the culprits. These outbreaks are often attributed to the compromised immune status of the fish. While research has been conducted in this area, several critical aspects still demand exploration. The need for species-specific dose standardization and efficient delivery methods is paramount. As the field is still in its early stages, there is substantial room for growth, and regulatory measures akin to those governing pharmaceuticals must be developed for the incorporation of nutraceuticals into aquafeed. Further studies are essential to delve into synergistic effects, nano-delivery systems, and the mechanisms of action of various nutraceuticals, with the ultimate aim of bolstering disease resistance and overall health in aquatic species. This research holds the key to enhancing the sustainability and productivity of the aquaculture industry.

Conclusion

Nutraceuticals, a diverse category of bioactive compounds, play a pivotal role in the health and productivity of fish in aquaculture. Among these, antioxidants shield fish from harmful free radicals, bolstering their immune defense and reducing disease susceptibility. Methyl donors are essential nutrients vital for DNA and RNA synthesis, while also supporting the metabolism of fats and amino acids. Immunostimulants fortify the immune system, making fish more resilient to diseases and mitigating the severity of infections. Probiotics, comprising beneficial microorganisms, enhance gut health, improving digestion, nutrient absorption, and safeguarding against ailments. Furthermore, herbal extracts encompass compounds that can alleviate stress, boost growth, and refine the taste of fish. While the application of nutraceuticals in aquaculture is evolving, ongoing research is vital for determining the ideal dosages and combinations tailored to different fish species, furthering our comprehension of their mechanisms and long-term effects. This growing body of knowledge holds the promise of advancing fish health and overall production in aquaculture.

Declaration of Competing Interest

The authors affirm that they do not have any known competing financial interests or personal relationships that might have influenced the work presented in this paper.

CRediT authorship contribution statement

Sagar Vitthal Shinde: Conceptualization, Data Curation, Original Draft Writing, Review & Editing. Shamika Shantaram Sawant: Conceptualization, Investigation, Writing - Review & Editing. Sagar Sitaram Rathod: Writing Review. Prakash Patekar: Writting. Samad Sheikh: Writing - Original Draft, & Editing. Swapnil Narsale: Review: Kapil Sukhdhane: Review & Editing. Indulata Tekam: writing

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