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Research Article

Mitigation of Stress in Fish through Nutraceuticals

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Abstract

Recently, there is a huge emergence of new technologies and products to provide an ideal environment for farmed fish. This will not only improve the income of farmers, but also important to address public health concerns. In this respect, large quantum of research emphasis has been given to amelioration of stress response in fish to improve growth and health. Also, there is an increasing interest of stakeholders in fish welfare. One of the environment friendly and user-friendly methods to ameliorate stress response is the incorporation of stress mitigating nutraceuticals in the diet. There is an interspecies variation among the fishes for stress responses. These studies enabled us to identify tolerant as well as sensitive species. This review focuses on the tolerance of fishes to most common stressors. As the stressors evoke different responses according to type of stress, duration of exposure and the species, the efficacy of nutraceuticals on mitigating their effect also will vary. However, ample of literature, is available on the effect of different nutraceuticals in different species which are already tested, with their specific mode of action. However, the specificity of the nutraceuticals was found to be more dependent upon the type of stressor rather than species. The functional as well as structural properties of those compounds have profound effect on the physiology of stress-exposed fish. In this article, the physiological effects of different stressors and the mitigating nutraceuticals are analyzed in the light of the evaluation of different stress biomarkers.

Keywords: Mitigation; Nutraceuticals; Stress; Fish; Biomarkers; Temperature

Introduction

Environmental factors are the one which decides the existence and distribution fishes in the water body. Physiology of fishes in many ways is directly affected by changes in environmental stressors. Stress is a state in which the lively stability of animal organisms called homeostasis is distressed by the actions of internal or external stimuli, generally defined as stressors. Stress is any situation that causes real or mental discomforts that consequence in a release of stresses associated hormone or specific physiological response. Between the several physical elements disturbing the aquatic ecosystem, temperature is the most important and is recognized as the 'a biotic master factor' for fishes [1]. Stress is existing in all living things and is the potency that brings about physical change and adjustment. Lower levels of stress can be harmless or even favourable, but higher levels of stress or extended periods of stress can create severe health problems. Stress can be either little and sudden or long lasting with chronic. When there is stress in fish, there is provocation of hypothalamus which causes stimulation of the neuroendocrine system and subsequently there is change in physiological and metabolic activity of fish. When there is any stress the concerning primary messenger brain-sympathetic-chromaffin cell axis and brain -pituitary-adrenal axis stimulate the uptake of more oxygen and mobilisation of energy substance, rearrangement of energy away from growth and reproduction and mostly suppressive effects on immunity functions.

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Stress indicators

Primary and secondary stress pointers are very valuable in evaluating the reactions related to particular aquaculture practices, or severe disturbances in the aquatic environment. Cortisol and catecholamine's are commonly measured as stress indicator [2]. Cortisol replies more gradually than catecholamines to particular stressors, it can be enumerated in research laboratory or field situations although the later delivers exact information about the reaction to acute stressors [3]. Post stress glucocorticoid levels can give data about specific stimuli (e.g., fish capturing stress, different holding and handling conditions, and serious exposures. Secondary stress indicators usually measured comprise of increase in glucose levels [2]; Lactate elevation, osmolality or specific ions, leukocytes [4]. Stress increases the permeability of surface epithelia (e.g. gill) to water and ions. This leads to higher circulation of catecholamine levels as well as structural damage to gill and skin as they are the main site of damage. Due to stress the level of cortisol increases then it combines with the glucocorticoid and mineralocorticoid action, as cortisol is vital for the renewal of hydro mineral homeostasis in concern with hormones such as prolactin (in freshwater fish) and growth hormone (in seawater fishes).

Effects of common stressors on fish

Temperature**:** Fishes can withstand a certain range of temperature, after which it produces thermal stress creating a substantial disturbance in the normal functions of existence [5]. It has been recognized that with increasing normal temperatures significantly disturbs the Critical Thermal maximum (CT_{Max}), Lethal Thermal maximum (LT_{Max}), Critical Thermal minimum (CT_{Min}), and Lethal Thermal minimum (LT_{Min}). Thermal tolerance limits in reply to fluctuating acclimation temperatures varies in different species [6]. However, [7] suggested that climatic changes are adapted by *Labeo* *rohita* embryos due to global warming up to 33°C, without hindering the process of reproduction and embryonic development.

As fish is a poikilothermic animal, any variations (ideal range) in the water temperature is supposed to be a persistent cause affecting functions and structures at all stages of living organization [8], triggering metabolic stress [7,9-11] and susceptibility to diseases [12]. The combined effect of thermal stress and infection causes augmentation of respiratory burst activity of macrophages in *Cyprinus carpio* [13] and reduction in growth rate [7,10]. Combined effect of chlorine and temperature affects tolerance capacity of *C. carpio* [14] and fails to obtain attained thermal tolerance in *L. rohita* spawns [7]. Long term exposure to increasing temperatures due to green house effect and environment temperature changes causes breathing stress and collapse of compensatory general adaptive syndrome. As the temperature is lowered, the breathing rate also decreased. Because of fishes are ectothermic (cold blooded) and their metabolism is affected by outside temperature. An increase in temperature will minimize the DO in the water and increase the metabolic rate of the gold fish, thus causing respiration rate to increase.

Thermal tolerance in different species

Thermal tolerance of *H. brachysoma* was assessed after 30 days of acclimatization by means of the Critical Thermal Methodology (CTM). Since the CTM excludes death as the experimental end point, it is a valuable way for approximating the thermal tolerances of threatened or endangered or fish species [15,16]. For estimation of thermal tolerance 72 fish were used for doing CTM test. Fish (12 per treatment; 6 per aquarium for CT_{Max} and CT_{Min} tests, respectively) adapted to a particular temperature were visible to constant rate (0.3°C per min) was achieved, which were designated as the CT_{Max} and CT_{Min}, respectively. For maintaining the desired DO levels, continuous aeration was provided and Losses of Equilibrium (LOE) were noted for each fish. Each fish was moved to their acclimation temperatures and observed for the next 24 h, until all fish were better. The thermal tolerance polygon was made by plotting the acclimation temperatures on the X-axis and the mean CT_{Max} and CT_{Min} values on the Y-axis [17]. The values of CT_{Max} and CT_{Min} were raised significantly with increasing acclimation temperature [18]. The robust relationship among the acclimation temperatures and the thermal tolerance level (CTM) of *H. brachysoma* recommends that adaptation of temperature is important for biological process in fishes and is reliant on the acclimation temperature. The ideal temperature can be accessed from the relation between Q10 and acclimation temperature [19]. Revealed that suitable temperature point where Q10 value starts to reduce with raising acclimation temperatures, which resembles to the ideal temperature for growth.

Heat shock response

All organism replies to heat stress by producing a set of evolutionarily preserved proteins called the Heat-Shock Proteins (HSPs) which are molecular chaperones, guard the cells against the accumulation of altered proteins and shows an important role in adaptation to body temperature [20]. The HSP70 was observed in all the tissues of fishes (brain, gill, intestine muscle, and liver). HSP70 band was noticed in the Western blots regardless of the optimum temperatures or after the heat-shock treatments. Thus, it was expected that the single HSP70 band signified both isoforms. The HSP70 level was significantly higher in the liver followed by in the muscle and brain and lowest in the gill tissue of fish, irrespective of the adaptable temperatures (20°C or 30°C). However, the level of HSP70 was significantly higher in the tissue of fish adapted at 30°C than those acclimated at 20°C.

Effect of temperature on reproduction

Temperature is a major physical, controlling factor in the survival of fishes and this effect is stated mainly in the regulation of all reproduction-related processes that involve from gamete formation, gametogenesis, their maturation, ovulation and spermitation, spawning, embryogenesis, hatching, to larval and juvenile development and survival [21]. And thus, the temperature change can have a detrimental effect on fish reproduction. At higher temperature Inhibitory effects occurs which result in conformational changes in proteins (e.g. FSH, LH and their receptors, steroid-synthesising enzymes) and also their rises affinity for steroid hormones to form water-soluble conjugates at increasing temperatures [22].

Thermal inhibition of reproduction in fishes can also occur due to catecholamine-mediated response, i.e. rise in plasma cortisol, prolonged level of cortisol showed suppressing plasma levels of T and E2 [23]. There are extensive reports showing that temperature also determines sex in fishes. Higher temperatures inhibit aromatase activity and drive sex determination towards the male phenotype [24]. A prediction here is that rising sea temperatures will upsurge the percentage of fish developing as male, even within the thermal range over which reproductive performance can be conserved. The higher temperature leads to hypoxia which may affect the reproduction and may lead to reduced population size of a species or extinction, which would result in an eco-biological disaster. However, [7] recommended that *L. rohita* embryos can tolerate climatic variations due to global warming up to 33°C, without effecting the reproduction and embryonic development.

Water temperature plays a major role in both initiation and termination of spawning season and control the melatonin production. Melatonin is the first signal of fish reproduction. Temperature have direct action on gametogenesis, Pituitary gonadotropin secretion, Metabolic clearance of hormone [25], Responsiveness of liver estrogen in the production of vitellogenesis, Responsiveness of gonad to hormonal stimulation [26]. Low temp favours the formation of primary spermatocytes (meiotic phase), but higher temp promotes spermatogonial proliferation and spermitation. Low temp promotes the early phase oocyte growth in case of marsh killifish. In rainbow trout low temp important to ovulation, otherwise the ova survive only a short time. In gulf croaker, ovulation and oocyte hydration is influenced by water temp above 17°C. Rise in temp is also implicated in the spawning.

Hypoxia

Hypoxia is one of the potential stressors associated with global warming and climate change in aquatic systems which refer to a dissolved oxygen level less than 2 mg•l-1. When the DO level drops below 1 mg•l-1, the water is known to be anoxic, or void of total oxygen [27,28]. Hypoxia may be a naturally occurring event commonly found in several parts of the world and is by the mixture of several physical factors. The major reasons for hypoxia are rise in temperature, stratification of water bodies, overcrowding, algal crash, poor water flow and aeration [29]. Both hypoxic and anoxic conditions may have detrimental effects on fish species. Most fish species are unable to acclimatize to drop oxygen concentrations which results in metabolic depression and finally lead to mortality.

Hypoxia tolerance

A fish's hypoxia tolerance can be represented in different ways. There are different ways to represent Fish hypoxia tolerance. Most common representation used among is the critical O_2 tension (P_{crit}), which denotes the lowest water O_2 tension (P_{O2}?) at which fish can sustain a constant O_2 consumption rate (MO_2). Fishes with a lower P_{crit} is more hypoxia-tolerant than a fish with a higher P_{crit}. Hence P_{crit} is often used to signify hypoxia tolerance, it often denote the ability to use environmental O_2 at hypoxic and avoids its significance towards the anaerobic glycolysis and metabolic suppression to hypoxia tolerance [30]. P_{crit} values were evaluated for a number of freshwater and marine species with higher number of cyprinids, which has been reviewed by [31]. An extreme tolerance to hypoxia, i.e., thriving in anoxic conditions was observed in common carp, crucian carp and goldfish [32]. Hypoxia tolerance by fish can be defined as the time spent at a particular hypoxic PO_2 before it loses dorsal-ventral equilibrium (called time-to-LOE), or the PO_2 level at will its equilibrium is disturbed when PO_2 is lowered from normoxia to anoxia at some set rate (called PO2-of-LOE). A higher time-to-LOE value or a lower PO2-of-LOE value therefore implies enhanced hypoxia tolerances. Another method to assess the hypoxia tolerance is median lethal concentration (LC_{50}). In *Cirrhinus mrigala*, a bottom dwelling major carp, the LC_{50} was found to be 0.28 mg/L^{-1} [33].

The effect of hypoxia on fish behaviour

Hypoxia can modify normal behaviour of fish. They increase surfacing reflex which is termed as Aquatic Surface Respiration (ASR). ASR during hypoxia is initiated by the action of O_2 chemoreceptors located in the gills which are responsive to both blood and water O_2 levels [34]. At the time of ASR, the snout and upper lip of fish protrude above the surface of water and often grasp air bubbles in the buccal cavity. This is supposed to raise the O_2 concentration of the water transient over the bubble and across the gills. ASR authorized the survival under hypoxic conditions which would else be fatal [35] and many of the behavioural adaptations for reproduction are also modified due to hypoxia such as fin fanning and surfacing of the young ones...etc. However, many behavioural adaptions increase the predation risk, especially during ASR [36]. ASR is a sustainable strategy in non-air breathing fishes as it can be employed for longer periods and can store ore oxygen in the blood than in the gills. Hypoxia mediated enhanced surfacing and gill ventilation in *Cirrhinus mrigala* [33].

Effect of hypoxia on cardiorespiratory, metabolic and molecular responses

There will be increased respiratory rate due to hypoxia as an acute response; however on the chronic exposure the respiratory rate progressively reduces and stabilizes, which has been demonstrated in *C. mrigala* However, the reduced respiration at chronic exposure was still higher than the basal respiratory rate [33]. Metabolic suppression is a common strategy to cope-up hypoxia, i.e., when there is low oxygen availability, reduces the oxygen demand by reducing aerobic metabolism. Thus, there will be an up regulation of anaerobic metabolic pathways such as glycolysis and reduction in TCA cycle flex [37]. All hypoxia responses in the body are mediated through the transcription factor, HIF-1α. It mediates the responses such as vasodilatation, metabolism, acid base balance etc. Also, haem concentration due to hypoxia for enhanced blood oxygen capacity was reported by several authors [38-40].

Effect of hypoxia on reproduction

The impacts of hypoxia on reproduction ranges from the delay in the gonadal recrudescence to the malformed embryos and larval mortalities. Hypoxia suppressed the expression of cyp19 gene which is responsible for the production of estradiol, and favoured male-dominated sex differentiation in zebrafish. Also, it is reported that natural fish populations in the hypoxia -afflicted areas become male dominated [41]. Recently, it is reported that hypoxia resulted in the transgenerational ill effects in the reproduction of fish [42].

Handling stress

Many of the handling stress symptoms are observed in broodfish-poor recovery of spent brood during post-spawning rearing phase. Physical stress in the brood is mainly caused during transportation of brood from pond to hatchery or vice versa. Besides, hormone administration, weighing operation etc., also causes stress to the broodstock. Some of these points are further elaborated with examples. When the workers transport gravid brood from pond to hatchery in a happa or in a container, they hurriedly keep too many numbers brood with very little water or even without water. The fish which remain at the bottom of the container, take the entire load of the stock. This may cause the internal haemorrhage to the ovary the female brood. Transportation of the limited number of brood in case of sufficient water in a hammock in a free-floating condition caused negligible stress to the brood. Hand nets or scoop s arc often used in hatchery to handle the brood. In an under-sized hand net and oversized mesh, the brood remains in a bent position projecting the paired and unpaired fins outside through the mesh. This causes injury to the fins and stress to the fish. Bigger hand net than the brood and smaller mesh size than the fin is always preferred for handling the brood.

Intra-muscular hormone administration is the common practice of induced breeding. In this operation, one person holds the fish tightly, and other injects the hormone content intramuscularly below the scale at the caudal peduncle. Intra-peritoneal administration on the thin scale less skin below the pectoral fin reduces the chance of stress. Makes the administration process much quicker and easy. In a breeding operation, the post-spawning sex play and chasing cause physical injury to the spent brood. Timely separation of both the sexes improves the situation.

Nitrite toxicity in fish

Nitrite is the product of feeding in aquatic systems and always results from the breakdown of ammonia. A build-up of nitrite in fish culture environment can lead to stress condition in fish and eventually serious production loss in aquaculture [43]. In aquaculture systems, for effective ways of controlling and monitoring stress, good knowledge of the response of fish to different stressors must be known, which in turn improves productivity. The organization of nitrite in aquatic systems is often unnoticed, giving more position to the controlling of ammonia. Ammonia and nitrite toxicity number of fish studies have recognized that one of the significant factors triggering substantial stress in fish is higher nitrite level in water [44]. Uptake of nitrite are through two routes, viz; Active uptake of nitrite in freshwater fish with the help of chloride cells of fish and a very minute quantity of nitrite may enter fish *via* diffusion of HNO_2, but this way seems irrelevant in most of the cases.

Physiological effects of nitrite toxicity

Nitrite is transitional in the oxidation of ammonium to nitrate, converts haemoglobin to methaemoglobin. Methaemoglobin cannot carry oxygen and hence results in anoxia to fish and other organisms in the aquatic environment. The anoxic conditions caused by methaemoglobin can effects several organs like liver and even retina. Also, it causes lysosomal and liver mitochondrial variations in fish subsequent it raises in the viability of these organelles. However, in the brain the methaemoglobin even at high levels neither causes a cerebral hypoxic condition nor alters the mitochondrial working. As a general thumb rule, methaemoglobin level greater than 50% are measured as threatening to fish [45]. The gills are vital organs in fish for respiration, ionic balance, osmotic regulation and nitrogenous waste excretion. In gills hyperplasia, increase in the number of chloride cells occurs due to nitrite toxicity. Hyperplasia will lead to neoplasia. Also, nitrite causes gill damage and damage of respiratory system and which leads to hypoxia and rise in LDH activity in tissues.

Nitrite can potentially affect cardiovascular functions. There is a speedy and determined upsurge in the heart rate due to vasodilation that is caused by nitric oxide produced from nitrite. It will lower the blood pressure by increasing the blood flow. The heart rate variability (i.e. variability in the time elapsed between sequential heartbeats) also decreases. The reduced heart rate variability may reflect the physiological deterioration. Also increase in the level of nitrite in fish causes loss of K+ from red blood cells which lead to increase in extracellular K+. The increase in the extracellular K+ is not favorable for the heart and other excitable tissues because it causes depolarization that can lead to heart failure and nerve malfunction.

Nitric oxide inhibits steroid hormone synthesis. It prevents cytochrome P450scc the primary and rate limiting phase in the pathway from cholesterol to steroid hormones [46]. Nitrite reacts with NH_2 and SH groups of amino acids, inhibiting several enzymes and producing nitrosamide-like compounds that are carcinogenic. Short-term exposure of nitrite affects the hematology and mineral ions in the fish's body. Therefore, it is very important that water quality stressors such as nitrite be monitored frequently and level should be controlled management practices when needed. Uncontrolled level of nitrite in culture environment may not lead to mortality but also prevent the fish from attaining in terms of growth and reproductive capability.

Pesticides toxicity in fish

Pesticides are constituents used to control harmful organisms, including insects, weeds, and plant diseases. Application of pesticides in cultivable areas to control different harmful pests is enormously toxic to other organisms which are not its target like fishes, and it affects their health through a deterioration of their metabolism, which ultimately leads to its mortality. Several researches have been conducted to study the effects of pesticide and insecticide toxicity in fish, and the results had shown that at chronic level, it causes varied effects such as oxidative damage, inhibition of Acetylcholinesterase (AchE) activity, histopathological changes in different tissues such as liver, gill, muscle, intestine etc. as well as whole body developing changes, mutagenesis and carcinogenicity [47,48]. Other visible symptoms of pesticide toxicity include alterations in swimming ability, reduced feed intake, disruption of schooling behaviour, changes in spawning patterns and increased stress. Significant decrease in the level of protein of liver, intestine, gill, muscle, gonad and blood was observed in several fish species exposed to pesticides [49,50]. Endosulfan is an organochlorine lipophilic pesticide extensively used in agriculture and related processes. This gets incorporated into the aquatic organism's food chain by ingestion or by straight interaction through skin or scales, gills and results to stressful surroundings to the aquatic fish fauna and causes blocking of neuronal Gamma Aminobutyric Acid (GABA) gated chlorine channels. Several studies on the toxicity of pesticide in fishes have shown diverse effects at chronic level, which includes oxidative damage, prevention of ACHE activity, variations in histopathological as well as embryonic developmental changes, mutagenesis and carcinogenicity. The capacity of pesticide to effect (to cause harm) the fish or other aquatic organisms depends on various factors like its toxicity, dosage rate, time of exposure, and its tenacity to remain in the environment. A lethal do called a lethal concentration 50 (LC50) needed to cause death meanwhile not all animals of a species die at the same dose, a standard toxicity dose amount, called as LC50). Bioavailability denotes the amount of pesticide available in the environment to fish. Some pesticides are rapidly breakdown after application. As various pesticides are breakdown rapidly after their application while some bind firmly with soil in the water column or to stream bottoms, thereby decreasing their accessibility. Some are quickly diluted in water or rapidly volatilize into the air and are low available to aquatic life. Bio-magnification refers to the accretion of pesticides at each consecutive levels of the food chain. Persistence of pesticides refers to the amount of time a pesticide is retained in the environment. This ability of pesticide how much time to degraded down is based on its chemical composition and environmental situations. Persistence is expressed as "half-life" (T1/2) of a pesticide [51]. Pesticides are degraded by sunlight (photo-decomposition), biological action (Microbial decay), windy air, water temperature, moisture and soil chemical composition (pH). Those pesticides which are slowly breakdown remain available for long time in aquatic environment.

Physiological effects of pesticides

Organophosphates and carbamate pesticides influence ACHE activity more than other contaminants. Due to prolonged exposure to organophosphate, the fish undergoes reduced swimming capacity and peroxidative damage in brain and gills. It has been found toxicity of Dichlorvos (organophosphate) causes alteration in DNA replication results in mutations and cellular Hypercellularity. At concentrations of 0.01 ppm, Dichlorvos generated chromosomal anomalies in view of centromeric gaps, chromatid breaks, chromatid gaps, attenuation, sub-chromatid breaks, pycnosis, extra fragements, etc. in kidney cells of *Corydoras punctatus* fish after exposed for time period of 24 hr, 48 hr, 72 hr and 96 hr [52]. The protein content in the liver, intestine, muscle, gills and blood of fish decreases due to exposure of Oleandrine (insecticide) and Endosulfan (*Channa* sp.).

In juvenile salmonids, the exposure to particular pesticides for long time causes upsurge stress and hence making them more vulnerable to predation. Pesticides vary in the movement of their motion which in turn causes a decrease in the ability to feed, to avoid predators, to guard territories, and to maintain the position in the river system. The immune system of fish can be even disrupted even exposure to Exposure to low concentrations of pesticides. At low concentrations pesticide act as mimics or blockers of sex hormones, causing irregular sex change, the feminization of males, irregular sex ratios, and rare breeding behaviour [53].

Aldrin, dieldrin, DDT, HBC and Chlordan (for 10, 20, 30 days/ carp fish) increased haemoglobin content, respiratory disruption occurred. Transformation in the colour of the gill lamellae from reddish to light brown, hyperactivity, loss of buoyancy, zigzag movement, elevated cough, loss of schooling behaviour, respiration near water upper surface, higher mucous secretion, head shaking and imbalance before death had also been observed [54].

Osmotic stress

Salinity is an intrinsic physicochemical property of water, indicating an amount of dissolved ionized salt. It influences thermodynamic properties of water (e.g., heat capacity, density, solvent capacity for solids and gases). Salinity stress influence both the fishes and the aquatic environment also. During the time of migration, the salinity stress is more as there is change in ions concentrations which also changes their physiological activities from the normal fishes. They adapt to this situation by changing some physiology of body processes. The salinity changes their biochemical processes both inside and outside the cell due to imbalance in the ions' uptake. The salinity of seawater is more than the body fluid of fish. So, the ions move continuously to the fish and water comes out from the fish body. They have to drink water continuously to maintain their body fluid osmolality. Changes in salinity levels affect fish directly or indirectly causing stress and induce a metabolic reorganization to meet the energy requirements of osmoregulatory organs of teleosts [55]. Salinity interferes with internal osmolality, ionic concentrations and cell volume which lead to increased expenditure of energy and retarded growth in aquatic organisms. When the fresh water fish *Tilapia mossambica* was exposed to enhanced salinity (iono-osmotic stress), its outcome was found even at the mitochondria isolated from muscle and gill tissues [56]. Salinity stress also showed other effects such as reduced Red Blood Cell count (RBC), White Blood Cell count (WBC), Hemoglobin (Hb), respiratory burst activity, total serum protein, albumin, and globulin levels, as well as serum lysozyme activity [57].

Osmotic stress during transfer between freshwater and seawater

When a fresh water fish is transfer to sea water there is increase in the drinking rate. This type of drinking response found in eels [58] returns to the normal level after few hours in sea water. When transferred to sea water, rainbow trout increase in drinking rate from about 0.5 ml kg -1h-1to over 25 mlkg-1h-1.). Other changes in the rainbow trout seen during these first few hours are dehydration of the whole-body results in weight loss.

During their first 8 hr after through transfer from fresh water to two-thirds sea water, juvenile rainbow trout show significant increases in the Na+ and Cl- concentrations of the blood plasma, whole body and muscle tissues. Chloride is most penetrating ions so more amount of chloride ions found in the intracellular compartments. Transfer to sea water is accompanied by a precise decrease in both the glomerular filtration rate and urine flow. It is reported a decrease in the urine production of rainbow trout from 3.44 mlkg-1h-1 in fresh water to 0.031 mlkg-1h-1 in sea water [59]. When a fish transfer from sea water to fresh water accomplished by a marked reduction in both Na+ and Cl-effluxes. The stenohaline marine fish, *Holacanthus ciliaris*, is able to survive many weeks in fresh water provided that the environment calcium concentration is increased to the range 5 Mm to 25 Mm litre-1 [60].

pH stress

Commonly, pH shock takes place when a fish is moved from one tank to another tank. Their body is very sensitive to the change in pH. Aquatic life is incapable to adjust to the abrupt variations and incapable to retain acid-base, ion concentration, and ammonia excretion [61]. Sudden pH change causes acute stress but if the pH remains for long term it causes chronic stress. High meaning (greater than 10.0) or low meaning (less than 4.5) pH values are inappropriate for most aquatic organisms. Juvenile fish and earlier immature stages of aquatic insects are enormously sensitive to pH levels lower 5 and may die at these low pH values [62]. High pH levels (9-14) can damage fish by damaging cellular membranes. A freshwater fish generally lives at Ideal pH around 7.4 in the wild while saltwater fish are adapted to pH around 6.5 in the wild. In Zebra fish pH shock causes secondary stress response [61]. The major Causes of acidification are presence of large industries iron and steel mills, glass manufacture, cement manufacture and Those industries that use large quantities of coal for fuel, are supposed to be the major source of sulfuric oxides, whereas, petroleum burning vehicles are the chief source of nitric oxides. Another reason is due to acid rain which contains carbonic acid and nitric acid [7].

Ocean acidification

Ocean acidification is regarded to be a grave hazard to marine organisms, particularly for calcifying species that require carbonate ions to form their shells and skeletons [63,21]. Increase in pCO_2 has also a straight physiological effect on aquatic species through disturbance of acid-base balance and limiting oxygen supply. Increase of pCO_2 in tissue causes acidosis which results in harmful effects to many cellular processes mainly protein synthesis ionic equilibrium, enzymatic synthesis, functioning and oxygen transport. To adjust this acidosis fishes use acid-base equivalent ion transport from the body to the environment, usually through the branchial epithelium, and to a minor extent, *via* the kidneys and intestine [64]. One of the potential impacts of acidification can decrease aerobic capacity and is basis of tissue hypoxia in fishes. One of the maximum dramatic global variations owing to human actions over the last half-century has marked upsurge in the occurrence and the extent of periodic hypoxia in estuarine and coastal marine environments. All over the world around more than 400 coastal hypoxic zones (dissolved oxygen, DO: less than 2 mg/L) covering a total area of approximately 250000 km^2 have been recognized [65]. There are extensive report on hypoxia that known to hinder reproductive performance of fishes. Hypoxia acts as endocrine disruptors in fishes, by inhibiting aromatase enzyme and thereby favoring masculinisation [65].

Physiological changes due to pH stress

Reproductive failure occurs due to acid stress which is indirectly associated to alter in calcium metabolism and to defective deposition of protein in developing oocytes. It seems that the 'no effect' in reproduction occurs at the level of pH around 6.5 [66]. When concentration of higher pH causes severe acid stress variation of gill membranes and/or coagulation of gill mucus occur and death due to hypoxia and lengthening of the water-blood diffusion distance. The acid stress results in imbalance of electrolyte homeostasis in fish but causes of low pH on osmotic permeability are mainly deficient. After fishes are exposed to acid stress, their blood pH goes down due to flux of H+ ions through gill membranes into the blood [67]. This process cause variations in trans-epithelial potential and permits opposite (blood to-water) diffusion of Na+ ions down an electrochemical gradient. Lowered ambient pH causes affect with gill calcium levels results in permeability to both H+ and Na+ ions. When the capability of the buffer mechanisms is outdone the blood, pH drops and of haemoglobin capacity to transport oxygen is reduced. Thus, the co-operativity of oxygen towards haemoglobin decreases, which allows more binding of carbon dioxide with haemoglobin [68].

Crowding stress

High stocking density is considered as a chronic stressor in aquaculture, causing elevation of plasma cortisol [2,69]. The increase in stocking density causes harmful effects like poor growth, development and higher chances of diseases in fish due to crowding. The consequences of higher stocking density include increased competition for food, differential growth, and increased build-up of harmful metabolites in the system, increased incidence of diseases, reduced survival, cannibalism in some species etc. which ultimately results in stress to the species [70].

Mitigation of stress by nutritional intervention

All the effects of climate change in fish cannot be averted however; certain adaptive and mitigation measures can alleviate the impact of these detrimental consequences. One of the strategies in this direction is the nutritional intervention or nutraceutical approach to mitigate different stressors in fish. Studies have shown that nutraceuticals stimulate defense systems in fish, even in stressed conditions, and they contrary the deleterious effects mediated by stress [10,68,71-74]. Dietary high protein has amending effects against various stressors. It is testified that complement of high protein (50%) and vitamin C (0.2%) reduces bio-accumulation and stress reactions due to endosulfan toxicity in *Channa punctatus* [72] and claw ablation stress in *Macrobrachium rossenbergii* [71]. However, dietary supplementation of L-tryptophan at least level of 1.36% reduced the crowding stress and enhanced growth performance in *Cirrhinus mrigala* fingerlings [68]. L-tryptophan has also been reported to have thermal stress mitigating in *L. rohita* fingerlings and reducing salinity and thermal stress in *L. rohita* juveniles and *Tor putitora* fingerlings [57]. Another study revealed that dietary vitamin E is effective in mitigating nitrite stress in *L. rohita* juveniles. On the other hand, dietary pyridoxine supplementation was found to have stress mitigating and immuno-modulatory effects in endosulfan exposed [10] and higher temperature exposed [74] *L. rohita* fingerlings [75]. Have tested methyl donors (choline, betaine and lecithin) in mitigating negative effects of endosulfan in *L. rohita* and found that betaine and lecithin help in ameliorating endosulfan induced stress and augments to normal health status of *L. rohita* fingerlings during culture period. Some nutraceuticals are not only having stress mitigating effects but also have role in enhancing thermal tolerance [73]. Reported that thermal tolerance of *L. rohita* fingerlings could be enhanced by supplementation of 100 mg pyridoxine per kg diet. While on the other hand, dietary microbial levan enhanced tolerance of *L. rohita* juveniles to thermal stress.

Studies have specified that nutraceuticals can trigger defense systems in fish, even in stressful situations, and therefore can opposite the harmful effects up to an extent mediated by stress [10,68,71-74]. Some of the promising nutraceuticals for aqua feed include microbial levan [76,77] L- tryptophan [68], vitamin C [72], pyridoxine [10], vitamin E [78], methyl donors [79] etc. Hence, future aqua feed formulation should go beyond the mere traditional one being used till now. The use of nutraceuticals as anti stress agents is of recent origin and many researches are carried out in this regard. But the scope for further researches and their field efficiency needs to be tested. Exploring the newer feed ingredients along with nutraceuticals for immune-modulation and stress mitigation of fish is the need of the hour for both qualitative and quantitative enhancement of aquaculture production.

Levans

Levans are a group of fructans, which are the polymers of fructose making a non-structural carbohydrate, in which the monomers are linked by β (2-6) bonds. Levans are found primarily in microbial products although they are found in various plants and grasses and are used as an ideal prebiotic and immune nutrient in aquaculture. Certain microorganisms such as *Bacillus subtilis*, *Bacillus polymyxa*, Aerobacterlevanicum, *Corynebacterium laevaniformans*, *Streptococcus* spp, *Pseudomonas* spp etc. are capable of synthesizing levans from sucrose based substrates. Dietary administration of microbial levan in fish and other animals such as rats had proven to be effective in the mitigation of stress and in improving immunity.

Gupta et al. [80] reported the stress mitigatory, protective and immunostimulant properties of dietary microbial levan in *Cyprinus carpio* fry exposed to sub lethal toxicity of fipronil [81]. Reported the reduction oxidative stress in rats fed with levan polysaccharide. The administration of dietary levan in diabetic rats led to several beneficial effects such as decrease in blood glucose level and an increase of Superoxide Dismutase (SOD), catalase and glutathione peroxidase activity of pancreas and liver. These results were confirmed using histological techniques. Reported the enhanced thermal tolerance and protection against thermal stress in *L. rohita* fed with 1.25% levan along with their diets.

Proteins and amino acids

The body of an organism maintains a moderately large free amino acid pool in the blood, even in the lack of an intake of dietary protein. This free amino acid pool ensures the continuous supply of individual amino acids to tissues for the synthesis of various metabolites such as proteins, neurotransmitters and other nitrogen-containing compounds. Amino acids are gluconeogenic substrates and are converted to glucose during conditions such as stress, starvation etc. and results in the depletion of amino acids in the amino acid pool. Hence adequate dietary supplementation of protein is inevitable under stressful conditions [82]. A high protein (50%) Supplementation with vitamin C (0.2%) diminishes bioaccumulation and stress problems due to endosulfan toxicity in *Corydoras punctatus* [72].

In another experiment, high protein (35%) and vitamin C (0.24%) was supplemented during regaining of claw ablated *Macrobrachium rosenbergii* to increase the regeneration of chelate claws [75]. It was found that high dietary protein and vitamin C had the capacity to temper stress due to chelate claw ablation and may improve the regenerative capacity of ablated claws of *M. rosenbergii* males. The results indicated that high protein diet improves the amino acid pool in the cells and act as substrate for gluconeogenesis which assistance in fighting stress due to claw ablation [71]. The role of free amino acids and other non-protein nitrogenous substances in the maintenance of cellular tonicity during exposure to hyperosmotic media has been investigated in flounders [83].

Tryptophan

The amino acid tryptophan which is the precursor of serotonin (5- hydroxy tryptamine) exhibits a stress mitigating effect [84]. L-tryptophan plays important role in growth, immune-modulation, immunity and disease resistance in stress mitigation has also been evaluated in *L. rohita* fingerlings reared under thermal stress and the results revealed that the dietary supplementation of L-tryptophan ameliorates thermal stress, augments growth and modulates immunity in *L. rohita* fingerlings [85]. Also, studies on the role of L-tryptophan in combating combined stress of temperature and salinity in *L. rohita* juveniles by [57] also showed encouraging results. Dietary supplementation of tryptophan (1.4%) improved the Specific Growth Rate (SGR), White Blood Cell (WBC) count, respiratory burst activity (NBT), total serum protein, albumin, globulin and serum lysozyme activity of *L. rohita* juveniles under thermal and salinity stress [86].

The role of dietary L-tryptophan in mitigating crowding stress and growth augmentation was studied in *Cirrhinus mrigala* fingerlings by [68]. This study proved an increase in weight gain, Specific Growth Rate (SGR) and Protein Efficiency Ratio (PER) in treatment groups as compared to the control. The biochemical parameters for stress such as blood glucose, plasma cortisol, Malate Dehydrogenase (MDH), Aspartate Amino Transferase (AST), Lactate Dehydrogenase (LDH), and Alanine Amino Transferase (ALT) exposed a declining trend with increasing level of dietary L-tryptophan [87]. The data obtained so far suggests that 1.4% tryptophan supplementation helps in mitigating combined stress due to temperature and salinity as well as augments growth, physiological status of selected hormones and modulates non-specific immune functions.

Tyrosine

Tyrosine is one of the non-essential amino acids and is also a precursor of catecholamines. Several studies suggest supplementation with tyrosine causes reduction from effects of stress and fatigue. The catecholamine neurotransmitters, norepinephrine and dopamine in the brain are exhausted under conditions of stress in animals [88]. Tyrosine supplementation alleviates the depletion of catecholamines and stress induced performance decline [89]. Acute exposure to cold acts as a physiological stressor and can harmful influence features of ability to perform such as memory. In humans, supplementation with tyrosine two hours prior to exposure to low temperature reverted performance to the level observed when ambient temperature was 22 degrees. Tyrosine supplementation also enhanced mood and memory in humans subjected to a combined stress of cold and hypoxia [90].

Glycine

It is the simplest amino acid and has a vital role in the osmoregulatory responses of fish and shellfish to environmental stress. Oysters rapidly absorb the free glycine from the nearby water, and they synthesize gill glycine in reply to rapid variations in salinity or anoxia. Glycine enrichment enhances survival of oysters after being moved from sea water to fresh water [91].

Miscellaneous amino acids

GABA (Gamma Amino Butyric Acid) is an amino acid neurotransmitter synthesized from glutamate found effective against hypoxia [92]. L-thiamine is an amino acid present in green or black tea. The levels of dopamine, serotonin and the inhibitory neurotransmitter glycine in the brain were increased as a result of L-theamine administration [93,94]. The use of green tea as a relaxing beverage is also renowned. Studies indicate that L-theanine can prompt alpha-brain wave activity, which resulted in a perceived state of relaxation. A study conducted by Japan reported that oral L-theanine administration of 200 mg led to amplified alpha-brain waves and a following sense of relaxation [95]. Presently no reports are available on the studies of stress mitigating effects of L-theanine in fish.

Methyl donors

Kumar et al. [75] have tested methyl donors (choline, betaine and lecithin) in mitigating the adverse effects of endosulfan and elevated temperature in *L. rohita* and found that inclusion of methyl donors in feed, especially betaine and lecithin help in ameliorating stress and augments the growth and health status of *L. rohita* fingerlings during the culture period.

Another study by [79] proved that dietary lipotropes, especially betaine and lecithin, help in mitigating oxidative stress due to exposure to low dose of endosulfan. The results of the experiment showed improved erythropoiesis, serum protein and lipid profile, antioxidant status, immune-competence, neurotransmission, and protective action on the livers of L. rohita fingerlings even when nonstop evident to low-dose of endosulfan.

Phosphatidylserine

Phosphatidylserine (PS) seems to have considerable anti-stress activity associated to its buffering effect on the HPA axis and adrenal cortisol production. It can beneficially modulate the endocrine responses by using a buffering effect on the high concentration of cortisol and ACTH in reply to physical stress. In studies conducted in subjects under stress, phosphatidylserine blunts the effects of cortisol and ACTH. Their action is counteracting stress induced activation of the HPA axis [96,97].

Fish oil

A research study carried on humans, found that with three weeks of fish oil supplementation @7.2 g daily in humans resulted in elevated plasma levels of cortisol and epinephrine. After three weeks of fish oil supplementation, it was found that, there was a significant reduction in the levels of cortisol and epinephrine is attributed to EPA and DHA present in fish oil [98]. The results of another experiment showed that EPA and DHA or DHA alone significantly reduces norepinephrine levels in healthy non-stressed individuals as well as students experiencing stress from taking exams.

Vitamins

Vitamins are organic molecules that act as cofactors or substrates in numerous metabolic reactions. They are usually essential in comparatively small amounts along with the diet and deficiency may result in disease or poor growth.

Vitamin C

In fish tissues, the anterior kidney, which comprises of adrenal tissue, functions as a storage site for vitamin C. Under stress, the ascorbic acid concentration of this tissue gets reduced rapidly with production of adrenal steroids simultaneously. Available evidence suggests ascorbic acid levels significant amounts can upkeep adrenal function and reduces high cortisol levels. Vitamin C acts as strong reducing agent in a number of reactions. Vitamin-C inactivates the damage due to free radicals formed as a result of normal cellular activity from various stressors and helps in regulating cortisol and prevents blood pressure from spiking in response to stress [99]. Vitamin-C was revealed to improve tolerance to environmental stressors and hypoxic stress. In humans, intravenous administration of a combination of ascorbic acid and vitamins B1 and B6 significantly improved the glucocorticoid function of the adrenal glands and at the same time normalized the rhythmic activity of the gland [100].

Fish and crustaceans have not capability of biosynthesis of vitamin C since they lack L-gulonolactone oxidase, which is key enzyme accountable for synthesis of vitamin C. Hence they require a dietary supply in adequate quantity in order to prevent the occurrence of deficiency symptoms such as reduced growth, poor wound healing, melanised lesions all over the collagenous tissue underlying the exoskeleton and eventually death.

A combination of both the vitamin C and E at double the normal dose was found to be able to maintain the different physiological, biochemical and haematological profile of *L. rohita* fingerlings when given to fenvalerate [71,78]. Reported that supplementation of combination of dietary high protein and vitamin C lessens stress due to chelate claw ablation and improved regenerative ability of ablated claws in *M. rosenbergii* males.

B-Complex vitamins

The B-complex vitamins have been commonly used as anti stress vitamins. Due to their contribution in energy production, they are essential to catalyze most anabolic pathways. The B vitamins are obligatory for steroid biosynthesis in the adrenal cortex [101]. Several studies have shown adrenal malfunction occurs with deficiencies of riboflavin (B2), pyridoxine (B6), biotin (B7) pantothenic acid (B5), and nicotinamide (B3) [102].

Vitamin B6 (Pyridoxine)

Administration of pyridoxine in feeds can boost production of serotonin and GABA which are essential for control of stress. Dietary pyridoxine exhibited roles in stress mitigation, immunomodulation and in enhancing thermal tolerance. Dietary supplementation of pyridoxine 100 mg/Kg diet resulted in immunomodulation and mitigation of stress due to endosulfan in *L. rohita* fingerlings [10]. The thermal tolerance of *L. rohita* fingerlings could be enhanced by supplementation of 100 mg pyridoxine per kg diet [73]. Dietary supplementation of pyridoxine at 100 mg/kg diet may opposite the negative effects caused by elevated temperature and was observed to protect the haemato-immunological status of *L. rohita* fingerlings reared at higher water temperature. Haemato- immunological parameters such as erythrocyte count, haemoglobin content, globulin, serum albumin, and lysozyme activity were found significantly higher in the treatment groups as compared to the control [74]. Reported dietary pyridoxine supplementation at the amount of 100 mg/kg diet augments growth and helps in lowering stress in *L. rohita* fingerlings reared at higher water temperatures. The inclusion of dietary pyridoxine had significant effect on growth performance and the activities of various anti-oxidative enzymes and stress parameters. The treatment groups exhibited higher Specific Growth Rate (SGR), lower activity levels of liver catalase, SOD of liver and gills, acetylcholinesterase of brain tissue and lower levels of blood glucose and cortisol.

Vitamin B5 (Pantothenic acid)

The functioning of adrenal cortex was found to be improved due to the administration of pantothenic in several experimental animal models. In the case of humans also, the administration of pantethine under stress conditions down-regulated the hyper secretion of cortisol [103].

Vitamin B12 (Cyanocobalamin)

In humans help to place back disrupted circadian cortisol rhythms back on schedule by shifting the cortisol secretion peak. Although methylcobalamin did not have direct influence on total levels of cortisol, indications recommends it might help shift the cortisol secretion peak, which aids in secretion at normal levels [104,105].

Vitamin E (Tocopherol)

In response to stress, Vitamin E has been revealed protection to the adrenal cortex from free radical damage and decrease cortisol production [106]. As an antioxidant, vitamin E has been found to defend the body from an extensive range of effects of free radicals [107]. A study by, revealed that nitrite stress in *L. rohita* juveniles can be effectively mitigated by supplementation of vitamin E along with diet. In this study, dietary supplementation with extra amounts of vitamin E was found to overcome the adverse effects of nitrite-nitrogen such as nitrite accumulation, effects on growth, haematological variables and ionic balance. The antioxidant enzymes have exposed that acute or chronic expo sure to stress upsurges free radical creation throughout the body but specific ally in the such as catalase and SOD activity was found to be significantly lower in the experimental group having maximum effect of vitamin E. The level of blood glucose was significantly lower in the groups supplemented with vitamin E, which indicates the role of this vitamin in mitigation of stress [108]. Detoxification effect of nitrite by met haemoglobin reductase system was boosted by dietary supplementation of extra quantities of vitamin E. Dietary vitamin E is also found to be effective in mitigating hypoxia mediated oxidative injury [109].

Vitamin A (Retinol)

Retinoic acid/retinol and carotenoid precursors are powerful antioxidants which have been shown to be important in the development of steroid hormones [110]. Reported that a diet scarce in retinoic acid fed to rats exhibited significant stunting of the adrenal cortex and did not produce normal amounts of corticosteroids which are involved in stress response. Vitamin A is also vital for the translation of pregnenolone into cortisol and even mild deficiency of vitamin A cause substantial diminishing of cortisol production [111]. Researches show retinoic acid or retinol to have an optimistic impact on adrenal health.

Minerals

Minerals or inorganic elements are required by animals to keep their metabolic functions and to afford materials for major physical elements. Some of the minerals are also found to have effects as anti stress agents. [112] studied the effect of supplementation of zinc picolinate (ZnPic) on, FCR, PER, SGR, feed intake, growth, and concentrations of Malondialdehyde (MDA), Zn, Cu, Mn, and ALP activity of rainbow trout. The results indicated a significant reduction of oxidative stress as a result of ZnPic supplementation. Elevated utilization of Selenium (Se) is found during stress and hence supplementation of Se in commercial diets can be required. Dietary Se supplementation in grouper, *Epinephelus malabaricus* reduced oxidative stress and improved the immune response of the fish. During stress Se status was more successfully conserved by Se-yeast than selenite [113]. Deficiencies, especially of magnesium, results in deleterious changes throughout the HPA axis [114]. A ratio of 1:1 calcium to magnesium is considered appropriate in cases of severe stress. Magnesium is an essential cofactor for stimulation of various processes and is specifically desirable to trigger and transport pyridoxine [115]. The essential micro-minerals, such as, manganese, zinc selenium, molybdenum, copper, chromium, and iodine acts against oxidative stress and are also significant cofactors for adrenal cortex role.

Nucleotides

The theory that dietary nucleotides might improve stress tolerance was first raised by [116, 117] observed that supplementation of nucleotides in the diet resulted in reduced levels of serum cortisol of rainbow trout after 90 days to 120 days infected with infectious pancreatic necrosis virus. In the case of challenged fish, enhanced disease resistance coupled with stress decrease linked with dietary nucleotides was also observed [118]. The nucleotides can partially diminish the negative effects of cortisol release linked with stress. Hence an exogenous supplementation causes increase in beneficial effects.

Antioxidants

An antioxidant molecule is capable of slowing down or preventing the oxidation. Antioxidants neutralize the free radicals produced during the stress there by preventing the damage to the cell. The antioxidants are mainly used as stress mitigators in fish nutrition. Supplementation of dietary bovine lactoferrin @1200 mg/kg diet enhances ability to air exposure stress and low salinity stress in orange spotted grouper, *Epinephelus coioides* [119].

Lipoic acid

Lipoic acid is regarded as superior antioxidant, which has been found effective to reduce the accretion of catecholamines during stress. It also improves the elimination of catecholamine degradation products [120]. Lipoic acid can partially restore the hydrocortisone-prompted suppression of helper T-cell activity and hence possess a beneficial effect when cortisol levels are high [121-132].

Conclusion

We should be prepared to face the challenges posed to us by climate change. Through proper physiological evaluation new candidate species can be found that can better adapt to the changing climatic conditions. Numerous techniques have been used to enhance the future of fisheries include considering the basic effect of climate change on living system at all levels of biological organization from basic molecular processes up to the ecosystem level. The nutritional interventions for stress management in fish in the facets of climate change consequences are a promising adaptive approach. However, further investigations especially in multiple stress mitigating measures are required to come out with a holistic dietary model to mitigate or adapt climate change effects.

Contribution

Showkat ahmad and Tincy Varghese carried out outline of the review study and written major portion of the review paper. Sanal Ebeneezar given his ideas and written some portion of the review article. Asim Kumar Pal edited and reviewed the article for major corrections and needed modifications of the review article. All the authors read and approved the final manuscript.

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