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REVIEW ARTICLE

Relationship Between the Productivity Losses of Tilapia and *Aeromonas Veronii* Infection

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Abstract

Nile tilapia (*Oreochormis niloticus*) is considered one of the top cultured fish in Egypt and the second globally. The high demand for animal protein was associated with intensive fish culturing, which resulted in the emergence of disease outbreaks causing significant losses in tilapia aquaculture among the recent years. With special reference to bacterial outbreaks, *Aeromonas veronii (A. veronii)* is a recently reported bacterial pathogen affecting farmed tilapia and other fish species worldwide. *A. veronii* has been notified as a significant threat on Nile tilapia populations resulting in heavy mortality and was recorded to have a wide range of antibiotic resistance. Subsequently, recent publications focused on immunostimulant alternatives. The previous science data on summer tilapia mortality phenomena were outlined in this review article with special reference to *A. veronii* as an important pathogen. Clinical and postmortem symptoms, histopathological lesions, genetic diversity, and associations with others submitted to GenBank, diagnosis, control steps, and significance to public health were highlighted.

Keywords: Tilapia, *Aeromonas veronii,* Summer Mortality.

Introduction

Aquaculture showed rapid growth in the last 30 years with the main role in maintenance of fish health and performance [1]. Globally, Egypt is ranked the ninth in aquaculture and from the largest fish producers in Africa as where aquaculture supplies many benefits in social and economic aspect [2, 3]. Kafr El-Sheikh, Behera, Damietta, Sharkia, and Fayoum considered the largest producer governorates share by more than 80% of the national aquaculture production [4].

Nile tilapia (*Oreochormis niloticus*) considered the second most valuable fish after carp and the most important cultured fresh water fish [5]. Nile tilapia has many advantages more than other fishes summarized in the following: (i) adapt easily to different environmental conditions, (ii) less susceptibility to diseases, (iii) eat wide range of food types, (iv) reared easily with other fish species with high stocking density, and (v) breed easily with no need for special hatchery techniques[5, 6]. Therefore, tilapia rearing has been moving towards intensification and development to meet the large demand [7]. This intensification with low health management care cause stress leads to spread of bacterial, viral, fungal, and parasitic diseases, which will be resulted in high mortalities and economic losses [8].

In the last years, the Egyptian tilapia fish farms are suffering from unknown cause mortalities that lead to great economic losses during summer [9]. Bacterial diseases are considered the most serious causes and one of the significant factors leading to huge annual losses in the fish culture industry that was estimated by billions of US dollars [10, 11]. There are two main categories of bacterial diseases, which reported as a pathogenic for fishes. The first

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category belongs to Gram-negative bacteria such as Aeromonas, Flavobacterium, Francisella, Pseudomonas, Edwardsiella, Vibrio, Yersinia, while the second one belongs to Gram-positive bacteria such as Streptococcus, Lactococcus, *Clostridium perfringens* and *Staphylococcus aureus* [10]. Despite the accusation of many of these species of bacteria in diseases of tilapia and other types of fish but, to the fact that the largest part of the cases that were recorded even in fish or human was caused by *Aeromonas* spp. [12].

From the most recorded motile aeromonads that causing 80 -100% mortality in fish farms are *Aeromonas hydrophila*, *A. caviae*, *A. sobria*, *A. jandei,* and *A. veronii* [13-17]. The ability to adapt to various trophic conditions and the ability to survive inside biofilms on different surfaces are one of the key factors for the proliferation of aeromonads in the aquatic enviroment [18, 19]. It is worth noting that Aeromonads is an opportunistic bacterium that attacks fiercely when there is any imbalance in the aquatic environment, such as high density or a change in water parameters and high temperatures[20, 21]. *Aeromonas veronii* infection is a hemorrhagic septicemia disease that is accused for massive tilapia fish mortalities in hot seasons in Egypt, Saudi Arabia, Thailand, India, and Malaysia [17, 22-25]. The pathogenicity of *A. veronii* is related to virulence genes and extracellular enzymes [26].

This review summarizes the currently available scientific data on tilapia industry in Egypt, tilapia summer mortality syndrome with reference to: (i) the most important etiological agents for summer mortality and their phenotypic and genetic characters, especially *A.veronii*, (ii) clinical, postmortem signs, and histopathological finding, (iii) Molecular diagnosis, and (iv) economic and zoonotic importance for this syndrome.

Tilapia industry in Egypt

Aquaculture was first introduced to the African countries in the 20th century, where its aquaculture production is ~2.7% with large-scale production were recorded in Egypt, Nigeria, Uganda, and Ghana [27-29]. Egypt is ranked 9th in fish farming production globally and 1stamong African nations [30]. The aquaculture industry in Egypt plays a crucial role in the country's economy, offering food security and work opportunities [31].

Nile tilapia is the major farmed fish, where Egypt is the second largest producer in the world after China [32]. Tilapia is categorized as one of the most popular fish species that is intensively cultured all over the world. Tilapia ranked the second most common farmed fish globally next to carps [33]. Globally, Nile tilapia, commonly known as the aquatic chicken, is one of the fastest growing aquaculture industries and the major cultured freshwater fish species [34]. The international tilapia industry was accounted to be 4.5 million tons in 2014 and is expected to reach to 7.3 million tons by 2030, supplying an inexpensive protein source in developing countries [29]. Tilapia fish represents 65.15% of the Egyptian fish production [4].

In the future, the tilapia industry is projected to increase due to its potential for disease resistance, resilience to diverse environmental conditions, its fast growth rate even at intensive culture, in addition, it is also an affordable source of protein [5]. Most of the coastal lagoons are located in the lower Delta, so utmost of tilapia fish farms development are concentrated in main four north governors Kafr El Sheikh, Port Said, Sharkia, and Beheira [4]. There are few studies that investigate the relation between fish farm development and low-income consumers demand to fish [35-37]. Furthermore, Murphy *et al.* [35] recorded the relation between Egypt's farmed tilapia markets, diversity and the different grades of product sold from where the prices according to size, quality, location, and market.

Tilapia summer mortality syndrome

Worldwide, fish diseases are among the most significant challenging obstacle in aquaculture sector and subsequently affect nutrition safety, food security, job availability, and human health [38]. Over the past five years, unexplained outbreaks of summer tilapia mortality have impacted the tilapia fish industry in Egypt and several countries around the world, with a detrimental effect on the productivity of tilapia farms [31]. Some previous studies have recorded several pathogens, whether bacterial, viral, or parasitic pathogens to be implicated in tilapia summer mortality outbreaks [9, 13, 17, 24, 25, 39-41]. In addition, the interaction between these pathogens and environmental factors during the summer seasons has certainly increased mortality rates. In addition, the increases in the consumer demand for the cheapest animal proteins, resulting in an intensification of fish farming, fish are exposed to several stresses, thus increasing the risk of disease exposure [31, 42]. Disease outbreaks, particularly by bacterial agents, remain one of the main obstacle factors that intimidate tilapia industry development, mainly under intensive culture [5]. Recently, Egypt witnessed unusual mortality reached 78.8% from which 96 to 100% were recorded in fish farms in Beheira, Kafr El Sheikh and Sharkia Governorates. Furthermore, 12 and 13% of farms notified uncommon mortality in the Faiyum and Minya, respectively. Beheira Governorate recorded the highest mortality (32.9%) and the lowest in Faiyum (3.5%), most of those mortalities were reported at the beginning of July by 62% of farms [31]. Fathi *et al.* [9] who recorded unexpected tilapia mortality through the summer season in the most significant Egyptian aquaculture governors (Kafr El Sheikh, Beheira and Sharkia). The mortality rate was around 9.2% with a vital economic impact approximate US$100 million, which may return to a multifactorial reason, but the actual cause remains unclear.

Bacterial agents implicated in summer mortality syndrome of tilapia with special reference to A. veronii

Outbreaks of mortality in cultured Nile tilapia can occur by certain bacteria or co-infection. Several studies recorded outbreaks threatening tilapia industry by certain bacteria, such as *Aeromonas* species[17, 22, 43], *Streptococcus* species[44-46], *Francisella* species [47, 48], *Edwardsiella* species[49]. Other summer tilapia outbreaks were resulted from co-infections. Co-infections are known by the multiple interaction between several pathogens and the implications for host [50]. On the base of the primary invader pathogens, it will be determined the degree of host susceptibility to the secondary infection, also determine the course, severity, and incubation period of the infection [51]. Taking in consideration stressors such as water temperature, limited dissolved oxygen, and high culturing densities have a significant role in the enhancement of fish susceptibility to pathogen invasion [41,42]. From the reported summer tilapia outbreaks, which were resulted from co-infections: Aeromonas in co-infection with other pathogens such as *Gyrodactylus cichlidarum* [41], Tilapia Lake Virus [13, 25] and *Streptococcus agalactiae* [52] or co-infection between *Streptococcus agalactiae* and *Francisella noatunensis* [53]. Also, several pathogens such as *Citrobacter freundii*, *Proteus vulgaris and Pseudomonas fluorescence* in mixed infection with *A. veronii* from several fish farm in Egypt were reported [24]. In Thailand, co-infection of multiple pathogens (*Flavobacterium columnare, Streptococcus agalactiae, Vibrio cholera, Plesiomonas shigeloides*, and *Irido virus*) with *A. veronii* was reported in Nile tilapia fingerlings outbreaks in August 2014 [54]. Moreover, *A. jandaei* and *A. veronii* were recovered from Nile tilapia juveniles with eye exophthalmia and turbidity with septicemic lesions in Thailand [17]. Another investigation in Egypt during September 2015 described the mixed infection between *A. veronii, A. hydrophila, A. ichthiosmia, A. jandaei, A. enteropelogenes,* and *Tilapia Lake Virus* showing symptoms of skin hemorrhagic lesions, loss of scales, ulcers, and dark pigmentation [40]. In Thailand and Vietnam 2012 *A. caviae*, *A. veronii*, and *A. jandaei* were isolated from diseased Nile tilapia exhibited signs of ascites, protruded eyes, and hemorrhagic lesions [55].

Aeromonas species as *A. hydrophila*, *A. veronii*, and *A. jandaei* are considered the major accused for increased mortality among wild and cultured fishes, resulting in massive economic losses [12]. *A. veronii* has recently been monitored as the common accused pathogen in outbreaks globally occurring in fish characterized by ulcerative syndrome in different fish species [22, 56, 57]. *A. veronii* is an opportunistic pathogen that may attack fish farms as a secondary infection or in immune disturbance cases as a result of stressor exposure [26, 57].

Susceptible species and life stages

A. veronii have been isolated from different species of fish for different life stages worldwide. Among the cases in which the infection by *A. veronii* was recorded around the world as follow: in China, the infection was recorded in channel catfish, long snout catfish, Siberian sturgeon, and loach fish [56, 58-61]; in India, the infection cases was reported in Oscar and fresh water ornamental fish [62, 63]. The *A. veronii* infection was recorded also in zebra fish in Korea [64]; guppy in Israel [65]. With regard to *A. veronii* infections in tilapia fish and its different species, cases have been recorded in Egypt [24,66,67], India [22], Saudi Arabia [23], Thailand [17, 54, 55], and in Malaysia [25].

With regard to infection and the different life stages, the previous studies have been documented *A. veronii* infection at the different age stages such as fry of grass carp [68], fingerling of tilapia [22, 24, 54], juvenile [25] and adult stage [24, 66, 67].

Seasonal prevalence

Recently, Nile tilapia has been suffered from phenomena of massive mortality outbreaks mainly in summer season. In 2015, about 37% of the Egyptian tilapia fish farms have faced unexplained summer mortality with an average 9.2%, which have great economic losses reached to US$100 million [9]. Youssuf *et al.* [24] documented 50:80% mortality outbreaks in Egyptian farmed Nile tilapia from 13 farms in different localities from April to October 2018. In the Eastern Province of Saudi Arabia, *A. veronii* were isolated from 31.07% of the examined fish and causes mortalities in reared Nile tilapia in the duration from January to December 2015 [23]. Eissa *et al.* [67] has recorded the higher prevalence of *A. veronii* during summer months (86.25%) in cultured Nile Tilapia in El-Sharkia Governorate, Egypt. In contrast, Hassan *et al.* [23] has reported *A. veronii* infection overall the year with higher incidence in winter months (45.71%) than summer ones (25.71%). In agreement with this result, a study was performed from January to March 2018 confirmed the higher incidence of *A. veronii* in Nile tilapia showing signs resemble streptococcal infection [22]. In Malaysia, *A. veronii* was successfully isolated from 50% of moribund red hybrid tilapia in May 2017, which suffering from massive mortalities [25].

Clinical signs and diagnosis

Clinical symptoms and postmortem lesions

*A. veronii*is is one of the fish septicemic diseases that contribute to high mortality rates and significant economic losses for the aquaculture industry. The naturally infected fish by *A. veronii* were externally characterized by sluggish movement, loss of appetite, loss of scales, dark skin pigmentation, corneal opacity, uni or bilateral exophthalmia, skin ulcers, and erythema [22, 66]. Some cases were characterized by hemorrhagic lesions throughout the body surface, opercular cover and fins base, anal opening protrusion with ascites as shown in Figure 1 [23, 25, 67]. Internally, the infected fish showed enlarged, congested, and hemorrhagic internal organs especially the hemopoietic organs (liver, spleen and kidney), enteritis[23, 55, 66] with enlarged gall bladder in some cases [25] (Figure 1).

Experimentally infected Nile tilapia with 9 X 10^8 *A. veronii* shown 80% cumulative mortality, skin black discoloration, loss of appetite with internal hemorrhage and hepatic congestion [66]. Some cases shown hemorrhagic internal organs, especially liver, kidney, and intestinal inflammation with mortalities up to 100 % within 24 h after artificial infection accompanied by a stressor such as transport-induced stress [17, 54]. Bilateral exophthalmia was observed in 70% of Nile tilapia experimentally infected intra-peritoneally by 3.2 × 10^7 colony forming unit (CFU)/fish with 100% cumulative mortality [22]. Other cases were reported to have signs and postmortem lesions in the experimentally infected fish more severe than the naturally infected, which characterized by external inflammation at the site of injection and hemorrhage on the skin and scales pocket with internal enteritis [23]. Besides, other signs were recorded such as abdominal dropsy, hemorrhagic ulcers on the body, reddening at anal orifice and fine bases, unilateral or bilateral pop eye, fin rot, and internal hemorrhagic fluids with congested organs [24] (Figure 2).

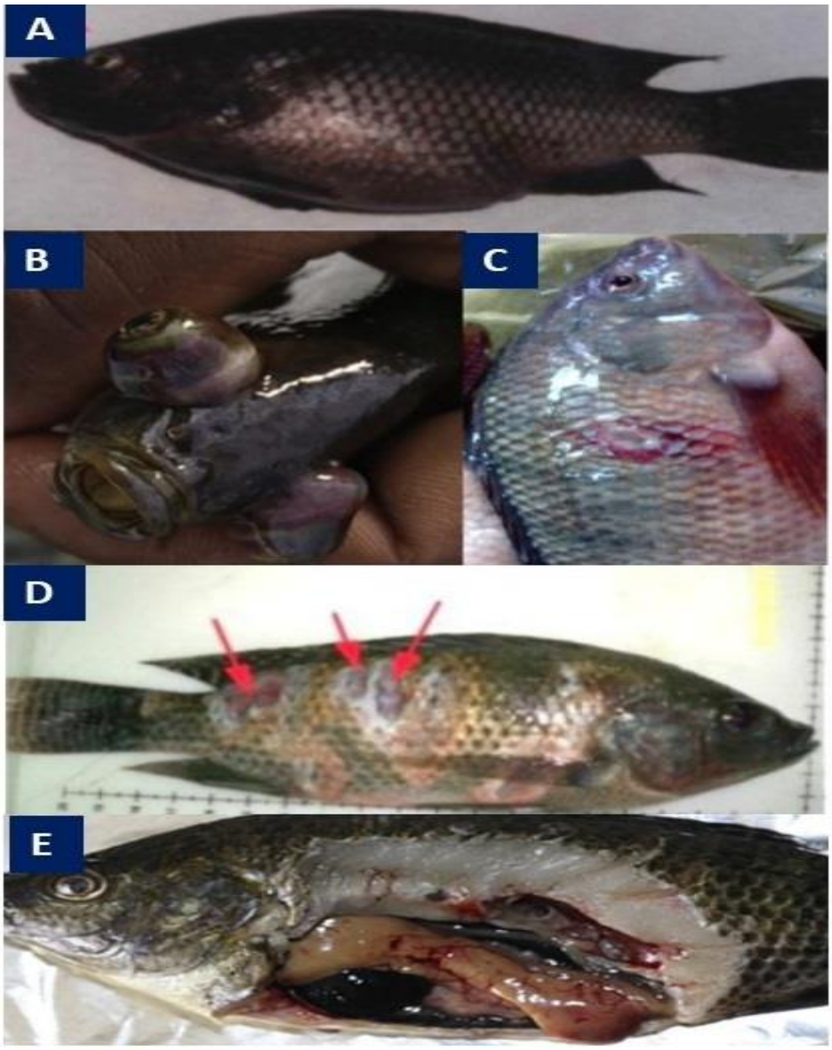

Figure 1: ***Oreochromis niloticus*** **naturally infected with** ***Aeromonas veronii*** **showing skin darkness and abdominal dropsy (A) [23], bilateral exophthalmia (B) [22],hemorrhagic ulcer (C) [67] and ulcerations varied in their degrees (red arrows) (D) [23]. enlarged liver and gall bladder and hemorrhages on liver (E) [22].**

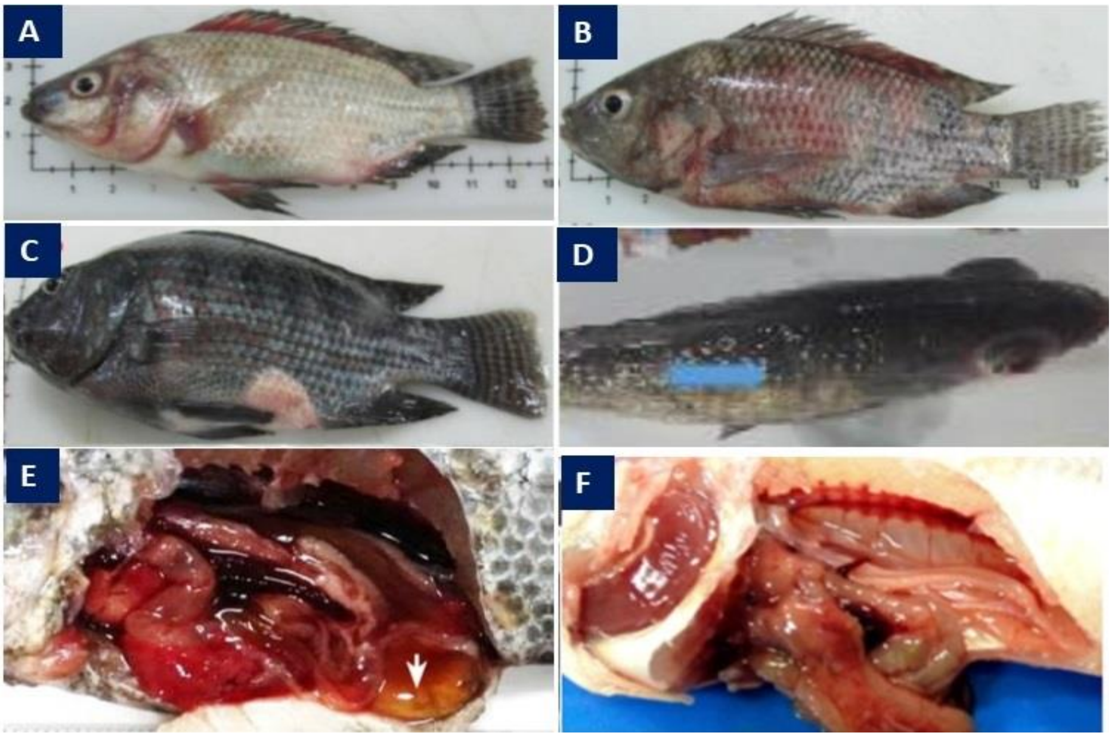

Figure 2: ***Oreochromis niloticus*** **experimentally infected with** ***Aeromonas veronii*** **showing hemorrhage at basal fins (A) [54], generalized external hemorrhage on fish body skin erosions (B), reddening and inflammatory reaction at the site of injection (C) [23], exophthalmia (unilateral and bilateral) (D) [24], yellow liquid accumulation in the swollen intestine (arrows) (E) [17], and hemorrhage in the liver (F) [54].**

Phenotypic properties of Aeromonas veronii

A. veronii has been described as Gram-negative, rod shaped, mesophilic, motile, and facultative anaerobic bacteria [69], that normally inhabitant in aquatic environment, sewage, food, and soil [70]. *A. veronii* colony in tryptic soy agar appeared as circular colony, which its diameter average from 0.9–1.1 mm, slightly elevated, shiny, and creamy to yellow color [23, 24]. While *A. veronii* grown as yellow colonies on Rimler-Shotts (RS) medium, and small, round, and dark green with dark center colonies on Aeromonas base media and not able to ferment lactose on MacConkey's agar as described by Abd El Latif *et al.* [66]. In conventional biochemical tests, *A. veronii* was indole, Voges-Proskauer, ornithine decarboxylase, citrate, β-galactosidase, gelatin-positive [17, 24, 66] and shows resistance to Vibrio-static reagent O/129 (150 μg ml^{-1}) according to Hassan *et al.* [23].

Several investigations spotted the light on the virulence factors, which responsible for *A.veronii* pathogenicity such as *caseinase*, *gelatinase*, *lipaseenterotoxins*, *alt*, *act*, *hemolysin*, *serine protease*, *aero*, *floR*, *sul1*, *qacED1*, *qnrS*, and *aada1*[59, 60, 65, 66]. *A.veronii* also characterized by its ability to multiply in a broad range of temperatures and salinity, to auto-aggregation and biofilm formation [65, 71]**.**

Genetic diversity of the Egyptian A. veronii strains and those from other countries

Recently, *A. veronii* sequences from isolates originating from Egypt, China, Bangladesh, Eastern Province (KSA), India, Israel, Malaysia, Thailand are accessible in the GenBank database (https://www. ncbi. nlm.nih.gov/gen bank/). The reported sequences identity among isolates originating from different continents has been recorded in Table 1. The basic local alignment search tool (BLAST) analysis of the 16S rRNA gene sequence of *A. veronii* isolates from Egypt or other countries showed identity % ranged from 97 to 100%. Dong *et al.* [17] who stated that genetic characterization of *A. veronii* isolated from Nile tilapia in Thailand are like that recovered from Nile tilapia in Malaysia.. While *A. veronii* that isolated from Malaysian hybrid red tilapia by Amal *et al.* [25] are closely related to *A. veronii* recovered from water of loach (*Paramisgurnusdabryanus*) culture in China.

Table 1. Overview of available *Aeromonas veronii* sequences in GenBank and the percentage nucleotide identity for sequences originating from Egypt and other countries.

Fish species (country)	Genbank accession number	Identity %	References
Nile tilapia(Egypt)	MK584926	100	[24]
Nile tilapia(India)	MH998019	100	[22]
Red hybrid tilapia (Malaysia)	MG283140	98	[25]
Nile tilapia (Thailand)	KP899499 - KP899504	99.9	[54]
Nile tilapia (Thailand)	KX714288	99.9	[17]
Nile tilapia(Thailand)	KU975017, KU975018, KU975021, KU975022	99.8	[55]
Longsnout catfish (China)	HQ434550, HQ540319 and HQ540320	97 - 100	[56]
Channel catfish (China)	GQ180116, GQ280902, KF761317 and KF761318		[58]
Guppy (Israel)	MF276645	99	[65]

Histopathology

Histopathological examination of moribund fish infected by *A. veronii* was reported in several papers from different organs including brain, spleen, liver, kidney, muscles, eye, gills, skin, and intestine (Figure 3). Liver of fish infected with *A. veronii* showed blood congestion and sever tissue necrosis and liver vessels were surrounded by hemosiderin, massive fatty changes with swollen hepatocyte [22, 66]. On other cases, hepatocyte and vacuolar degeneration with congested sinusoid were reported [23, 72]. Kidney of fish infected by *A. veronii* showed glomerulus congestion with moderate degenerative alterations in renal tubules combined with absence of nuclei and pyknosis, while in other cases necrotized renal tubules and glomerular destructions were recorded [22, 66, 72]. Other studies recorded only mild vacuolar degeneration in epithelial lining of some renal tubules [23]. Spleen was congested and hyperemic with marked degenerative alterations [17]. Spleen hemopoietic tissue depletion has been widespread in some cases [23]. Sometimes the spleen may show focal hemorrhages with proliferating lymphocytes [25]. The intestine showed epithelium necrosis, sloughing and hemorrhage [17]. Inflammatory exudates between secondary lamellae are seen in the gill section [22]. Regarding the brain, the main observed histopathological alteration is focal inflammation in the leptomeninges and congestion of blood vessels [25]. Whereas, Raj *et al.* [22] described sensory retina separation from epithelium retinal pigment.

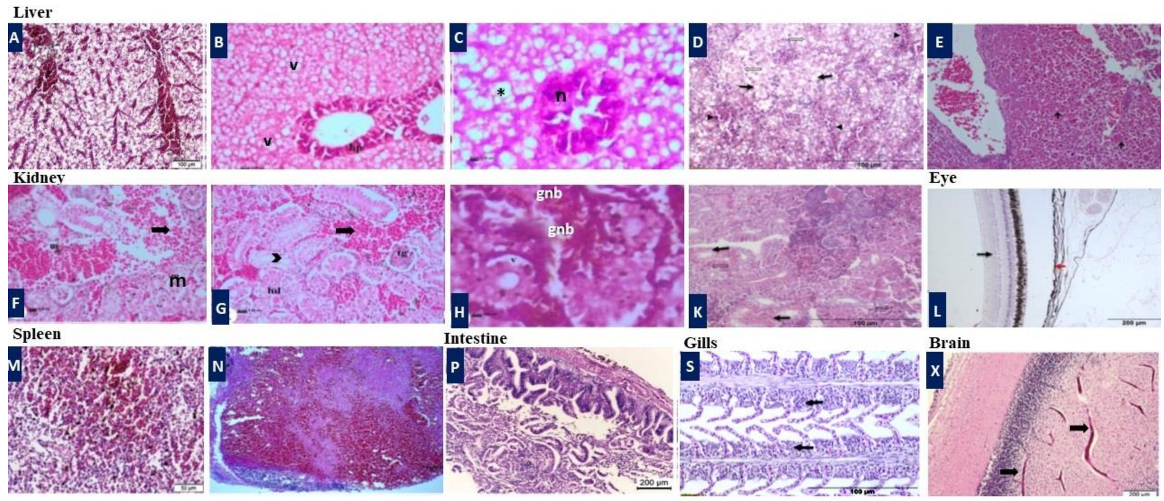

Figure 3: Histological changes of *Oreochromis niloticus* tissues infected with *A. veronii*. Liver: showing severe blood congestion (A) (H&E, 100 µm) [17], B: vacuolar degeneration of the hepatocytes (v) (H&E) [23], C: showing vacuolar degeneration (*) and necrosis (n) around the area of hepatopancreas (H&E) [23], D: severe fatty changes (black arrows) with hepatocyte necrosis (line arrow) along with sinusoidal congestion (arrowheads) (H&E, 100 µm) [22], and E: focal area of hepatocellular swelling and presence of syncytial hepatitis cells (arrows) (H&E, 200 µm) [25]. Kidney: showing interstitial hemorrhage (F) (arrow) and melanophores aggregation (m) (H&E) [23], G: vacuolar degeneration of the epithelium lining renal tubules (head of arrow), hemorrhage (arrow), thickening of glomerular capillaries' basement membrane (tg) and hyaline droplets (hd) in the lumen of some renal tubules (H&E) [23], H: multiple Gram-negative bacilli (gnb) in the renal tissue (Stained with Gram stain)[23], and K: mild degenerative changes along with loss of nuclei (black arrows) and pyknosis (line arrows) (H&E, 100 µm)[22]. Eye (L) showing detachment of sensory retina (black arrow) from retinal pigment epithelium (red arrow) (H&E, 200 µm) [22]. Spleen (M) exhibited hyperemia and hemorrhage (H&E, 50 µm) [17], focal hemorrhages with proliferating lymphocytes (H&E, 100 µm) (N) [25]. Intestine (P) showed epithelial cell damage and sloughing into gut lumen (H&E, 200 µm) [17]. Gills (S) exhibiting inflammatory exudate between secondary lamellae (arrows) (H&E, 100 µm) [22]. Brain (X) showing severe blood congestion occurred in the brain (H&E, 200 µm, respectively) [17].

Disease control measures

The unaware application of antibiotics as a magic tool for disease control in aquaculture sector led to the appearance of antimicrobial resistance phenomena, which subsequently threaten the public health. Therefore, the recent research pays their interest to the environmentally friendly alternatives to antibiotics for the microbial infection control such as natural herbs, probiotics, immunostimulants and others [73].

There were numerous studies for treatment of *A.veronii* infection in tilapia fish species (Table 2). From these, the study of Elabd *et al.* [74] who recorded *Astragalus membranaceus* nanoparticles (ANP) at 2% kg^{-1} diet had significantly enhanced lysozyme and nitric oxide (NO) activities, as well as improved superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities, interleukin 1, beta (*IL-1β*) genes expression after 30 days of feeding. Abdelghany *et al.* [75] testified the vital effects of dietary microalga, Nannochloropsis oculata (NP) at a concentration of 5% medicated feed on immunity enhancement and disease resistance of Nile tilapia against *A. veronii*. Sewaka *et al.* [76] studied the efficacy of synbiotics medicated diets which resulted in improved growth performance, biochemical, and immunological parameters mainly against *A. veronii* in juvenile red tilapia. Also,Yilmaz [78] reported that caffeic acid especially at 5 g kg^{-1} has increased Nile tilapia resistance against *A. veronii* as a result of the significantly increased phagocytic index, potential killing activity, respiratory burst activity, serum myeloperoxidase activity and serum CAT activity. Furthermore, increased levels of immune expression [*HSP70*, *IL-1β*, *TNF-α*, CC-chemokine (*CC1*), *IL-8*, toll-like receptor 7 (*tlr-7*), *IFN-γ* and *IgM*] and antioxidant related genes [*SOD*, *CAT* and *GPx*] were observed. Crude glucan (Cr-glucan) is one of the alternatives used also, which gave good results in increasing the resistance of tilapia fish against *A. veronii* as documented by Chirapongsatonkul *et al.* [79].

Aeromonas veronii was treated in other fish species using various medication trials. An Indian research was done in *Xiphophorus hellerii* using silver (AgNPs) and zinc oxide (ZnONPs) nanoparticles at 1 mgL^{-1} concentration for evaluation their effectiveness against *A. veronii*. They showed 83.3% and 100% survivability in infected fish, respectively [80]. A novel antagonistic bacteria named *Streptomyces flavotricini* X101promoting growth rate and survivability of grass carp after a month feeding at concentration of 900 μgmL^{-1}[81]. An investigation was done using selenium reported that 1 and 2 $mgkg^{-1}$ concentration have ability to enhanced growth and immunological performance, increase resistance against *A. veronii* and limitation of multiple stresses in *P. hypophthalmus* [82]. Sewaka *et al.* [76] recorded the therapeutic effect of *Lactobacillus rhamnosus* GG supplemented diets against *A. veronii* in juvenile red tilapia. Vaccination is regarded as an important alternative strategy for combating A. veronii, as shown by numerous studies. From these vaccines, live attenuated vaccine Δ*his*J [83], recombinant *Lactobacillus casei* expressing OmpAI [84] and recombinant *Lactobacillus casei* expressing flab [85].

Zoonotic importance

Latest literature confirmed that four species of Aeromonas (*A. veronii*, *A. hydrophila*, *A. caviae* and *A. dhakensis)* were responsible for 95.4% of human clinical cases and *A. veronii* alone sharing with 21.54% of total Aeromonas infections [86]. The highest incidence was recorded in children, elderly people suffering from hematologic malignancies or hepato-biliary disease and immunocompromised individuals [70, 87, 88]. According to Janda *et al.* [89] *A. veronii* was the most famous pathogen suspected of being the pathogen among the 7 Aeromonas species recognized by human infection.. *A. veronii* adding to the critical value of public health as previously stated in many articles [70, 90, 91]. Several investigations recorded the significant impact of *A. veronii* on human health resulting in signs such as septicemia, kidney disorders, pulmonary disorders diarrhea, and gastroenteritis [92-95]. Additionally, Ko *et al.* [96] recorded a case exhibiting variety of clinical symptoms, including gastroenteritis, pneumonia, infection of the hepato-biliary tract, infection in the skin and soft tissue, empyema, septic inflammation in joints, osteomyelitis, meningitis, endocarditis, and bacteremia. Furthermore, another non-traumatic case of old woman suffering from progressive pain with right shoulder joint immobility was recorded in china was found to be due to *A. veronii* infection[97]. Similarly; Roberts *et al.* [98] had recorded case report in an immunocompetent 81-year-old man developed septic arthritis and bacteraemia with *A. veronii*. In Bangladesh, Kühn *et al.* [99] reported a case suffering from cellulitis, peritonitis, meningitisand respiratory tract disorders due to *A. veronii* infection. Joseph *et al.* [100] documented an exudate formed after aquatic contact under the left eye of a 10-year-old male from previously infected wounds, which was cultured and revealed two different *Aeromonas spp.* (*A. jandaei* and *A. veronii)*. McKenzie *et al.* [101] reported a remarkable and un-common case of *A. veronii* septicemia, secondary to a drilling

Table 2. Alternative approaches to antibiotics for treatment and control of *A. veronii* infection in Nile tilapia and other fish species

Treatment	Fish Species	Dose and route of administration	Duration	Immune-Stimulatory Role	Reference
Astragalus membranaceus nanoparticles (ANP)	Nile tilapia	1, and 2%kg^{-1} diet	30 days	Significantly enhanced lysozyme activity and NO activities, as well as improved SOD, CAT, and GPX, *IL-1β*genes.	[74]
Nannochloropsisoculata (NP)	Nile tilapia	5, 10, and 15% in diet	60 days	Significantly improved serum lysozyme activity, NO, and NBT levels with significant upregulation of cytokines (*IL-1β, IL-8, IFN-γ, TGF-β and TNF-α*).	[75]
Black mulberry *(Morus nigra)*	Nile tilapia	0.75%, 1.5%, 2.0%, and 3.0% in diet	60 days	Increased activities of serum lysozyme, MPO, SOD and CAT, and increased the expression levels of immune-related genes [*IL-1β*, *TNF-α*, *IgM*, *IFN-γ* and *HSP70*] and antioxidant-related genes (*SOD*, *CAT*, and *GPX*).	[77]
Caffeic acid	Nile tilapia	1, 5, 10 g kg^{-1} in diet	60 days	Caffeic acid especially at 5 g kg^{-1}significantly increased phagocytic index, potential killing activity, respiratory burst activity, serum MPO activity and serum CAT activity. Furthermore, increased levels of immune expression [*HSP70*, *IL-1β*, *TNF-α*, *CC1*, *IL-8tlr-7*,*IFN-γ* and *IgM*] and antioxidant related genes [*SOD*, *CAT* and *GPx*].	[78]
Crude glucan (Cr-glucan) and commercial β-glucan from *Saccharomyces cerevisiae* (Yb-glucan)	Nile tilapia	10 µg fish^{-1} by intraperitoneal injection	24h	Cr-glucan developed the immunity that protect Nile tilapia from *A. veronii* infection	[79]
Jerusalem artichoke(JA) and *Lactobacillus rhamnosus* GG (LGG)	Red tilapia	10.0 JAg kg^{-1} diet, 10^8 CFU g^{-1} LGG diet and 10.0 JA g kg^{-1} +10^8 CFU g^{-1} LGG diet.	30 days	JA and LGG enhanced gut mucosal immunity and lysozyme activity against *A. veronii* challenge in red tilapia	[76]
Silver (AgNPs) and zinc oxide (ZnONPs) nanoparticles	*Xiphophorus hellerii*	0.5, 1,5 and 10 mgL^{-1}intramuscular and bath dip	48h and 96h	enhance the survival rate of 83.3% in AgNPs and 100% in 1 mgL^{-1} of ZnONPs	[80]
Selenium	*Pangasianodonhypophthalmus*	1 and 2 mgkg^{-1} diet	60 days	Increased anti-oxidative status in different tissues, and immunological status.	[82]
Recombinant*Lactobacillus casei*	Common carp	10^9 CFUg^{-1} diet"Oral vaccination"	66 Days	The recombinant vaccine candidate stimulated high serum or skin mucus specific antibody titers and induced a higher lysozyme, ACP, SOD activity with upregulation to*IL-10*, *IL-β*, *IFN-γ*, *TNF-α* genes expression.	[84]
Recombinant *Lactobacillus casei*	Common carp,	2 × 10^9 cells in diet	58 days	The recombinant *L. casei* was effectively induce humoral immunity, increase the serum immunological index, leukocytes phagocytosis percentage with significant increase of *IL-10, IL-β*, *IFN-γ* and *TNF-α*genes expression.	[85]

NO=nitric oxide ,SOD=superoxide dismutase, CAT= catalase, GPX= glutathione peroxidase, MPO= myeloperoxidase,IL-1β=interleukin 1, beta, TNF-α=tumor necrosis factor alpha, IFN-γ=interferon gamma, NBT= nitroblue tetrazolium, IL-8=interleukin 8, TGF- β=transforming growth factor-beta, IgM=immunoglobulin M, HSP70=heat shock protein 70,tlr-7=toll-like receptor 7, CC1=CC-chemokine,ACP=acid phosphatase activity, AgNPs =Silver, and ZnONPs=zinc oxide nanoparticles, JA=Jerusalem artichoke, LGG=*Lactobacillus rhamnosus* GG injury in an immunocompetent 29-year-old man without any significant past medical history. In Taiwan, *A. hydrophila* and *A. veronii* were implicated in a case suffering from empyema with fever, dyspnea, and pain in the chest [102]. *A.veronii* have been confirmed to have a significant impact on consumer health as foodborne pathogens [100, 103-105].

Conclusion

A. veronii is an important fish pathogen causing mass mortality of Nile tilapia during the summer months. For the control of this disease, the determination of the virulence genes associated with disease outbreaks and successful therapeutic compounds are necessary. It's important to find out therapeutic alternatives for minimizing the risk of antibiotics use and the antimicrobial resistance.

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Conflict of interest

The authors declare that there is no conflict of interest.

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الملخص العربي

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يعتبر البلطي النيلي من أفضل الأسماك المستزرعة في مصر والثاني على مستوى العالم. ترافق ارتفاع الطلب على البروتين الحيواني مع الاستزراع المكثف للأسماك مما أدى إلى انتشار الأمراض التي تسببت في خسائر كبيرة في تربية الأحياء المائية للبلطي خلال السنوات الأخيرة. مع إشارة خاصة إلى تفشي الامراض البكتيرية، فإن الايروموناس فيروني هو أحد مسببات الأمراض البكتيرية التي تم الإبلاغ عنها مؤخرًا والذي يؤثر على البلطي المستزرع وأنواع الأسماك الأخرى في جميع أنحاء العالم. في الآونة الأخيرة ، تم الإبلاغ عن الايروموناس فيروني كتهديد كبير على تجمعات البلطي النيلي مما أدى إلى حالات نفوق عالية. ولقد تم الاشارة الي تفشي الامراض البكتيرية عامة ،و الايروموناس فيروني خاصة كأحد مسببات الأمراض البكتيرية التي تم تسجيلها مؤخرًا والتي تؤثر على البلطي المستزرع وأنواع الأسماك الأخرى في جميع أنحاء العالم. ان الايروموناس فيروني يمثل تهديد كبير على البلطي النيلي والذي يؤدى إلى نفوق شديد بالاضافة الي مقاومته الواسعه للمضادات الحيوية. وعليه لقد ركزت الدراسات الحديثة على استخدام رافعات المناعة كبدائل.. تلخص هذه المقالة مجموعة من البيانات العلمية السابقة عن ظواهر النفوق الصيفي للبلطي مع إشارة خاصة إلي الايروموناس فيروني كمسبب ممرض مهم مع تسلط الضوء على علاماتها السريرية وعلامات ما بعد الوفاة ، التغيرات النسيجية المرضية ، والتنوع الجيني والعلاقة مع العزلات الاخري التي تم تحميلها على الجين بنك ، والتشخيص ، وتدابير التحكم ، والأثر الاقتصادي لذلك وأهميته علي الصحة العامة.