Int Aquat Res (2025) 17:1–15
https://doi.org/10.22034/iar.2025.2008914.1732

REVIEW

Promoting sustainable aquaculture: exploring antibiotic alternatives to fight against pathogens

Saima Mukhtar . Syed Makhdoom Hussain . Shafaqat Ali . Ebru Yilmaz . Muhammad Mudassar Shahzad . Muhammad Munir . Nadia Nazish . Mohammad Ali Alshehri . Adan Naeem . Muhammad Amjad . Zeeshan Yousaf . Eram Rashid

Received: 07 August 2024 / Accepted: 13 January 2025 /

Abstract Aquaculture, a rapidly expanding industry, provides a diverse range of protein sources. However, disease outbreaks can significantly impact production, leading to the use of antibiotics to mitigate financial losses. Nevertheless, the overuse of antibiotics in aquaculture poses significant environmental and public health risks, contributes to antibiotic resistance, and disrupts fish metabolism. The rise of multidrug-resistant microorganisms demands the creation of innovative, alternative therapies. This comprehensive review aims to identify and evaluate the efficacy of alternative approaches for combating pathogens in aquaculture, focusing on sustainable and environmentally responsible practices. Promising alternatives include immunotherapeutics, vaccinations, probiotics, prebiotics, herbal plant-based interventions, organic acids, bacteriophages, and quorum quenching. By exploring these innovative approaches, this review endeavors to promote the development of sustainable aquaculture practices that prioritize environmental stewardship, animal health, and human well-being.

Keywords Antibiotics . Antibiotic resistance . Disease prevention . Alternative treatment

Introduction

Aquaculture is a diverse and complex industry, encompassing a wide range of practices, from small-scale, traditional pond-based systems to large-scale, technologically advanced operations producing high-value aquatic species. The significance of aquaculture has grown rapidly over the years. In the

---

Saima Mukhtar . Syed Makhdoom Hussain (✉) . Adan Naeem . Muhammad Amjad . Zeeshan Yousaf . Eram Rashid
Fish Nutrition Lab, Department of Zoology, Government College University Faisalabad, Punjab 38000, Pakistan
e-mail: drmakhdoomhussain@gcuf.edu.pk

Shafaqat Ali (✉)
Department of Environmental Sciences, Government College University, Faisalabad, Punjab 38000, Pakistan
e-mail: shafaqataligill@gcuf.edu.pk

Shafaqat Ali
Department of Biological Sciences and Technology, China Medical University, Taichung 40402, Taiwan

Ebru Yilmaz
Bozdoğan Vocational School, Aydın Adnan Menderes University, Aydın, Turkey

Muhammad Mudassar Shahzad
Department of Zoology, Division of Science and Technology University of Education Lahore, Punjab 38000, Pakistan

Muhammad Munir
Date Palm Research Center of Excellence, King Faisal University, Al-Ahsa 31982, Saudi Arabia

Nadia Nazish
Department of Zoology, University of Sialkot, Sialkot, Punjab 51040, Pakistan

Mohammad Ali Alshehri
Department of Biology, Faculty of Science, University of Tabuk, Tabuk, 71491, Saudi Arabia

1980s, Asian countries, which currently account for 89% of global aquaculture production, drove the industry's expansion to meet the demand for aquatic products (FAO 2019). Aquaculture has shown unprecedented growth, surpassing other food production sectors globally. Recent estimates from 2020 indicate that global production of farmed food fish has reached 82.1 million tons, highlighting the ongoing importance of aquaculture in developing improved animal protein sources (Pradeepkiran 2019; FAO 2020). Aquaculture systems operate in diverse environments, including brackish, freshwater, coastal, riverine, saltwater, and terrestrial locations, spanning temperate to tropical climates. The industry farms a variety of species, such as seaweeds, mollusks, crustaceans, and finfishes, using extensive, semi-intensive, and intensive farming techniques. Farming practices utilize a spectrum of feed inputs, from natural to formulated diets, resulting in a variety of products from high-value finfish to low-value invertebrates (Bondad-Reantaso et al. 2005; 2023).

The growth of intensive aquaculture practices has led to environmental pollution, disease outbreaks and slowed fish growth, resulting in significant economic losses (Lafferty et al. 2015). The industry faces numerous challenges, including dissemination of infectious diseases, emergence of novel pathogens, escalating disease severity, and the far-reaching consequences of globalization. Additionally, aquatic animals cohabitate with a diverse range of microorganisms, which can include pathogens that pose health risks. The presence of these microorganisms depends on factors specific to the pathogen, host, and environment. To mitigate these risks, controlling the aquaculture environment is crucial. However, the selection of suitable control methods depends on various considerations, including the target species, economic viability, and existing infrastructure at national and commercial levels. In aquaculture, antibiotics play a vital role in preventing and treating bacterial infections (Selamoglu 2018). Most antibiotics target gram-negative bacteria, which are responsible for most bacterial illnesses in aquatic animals. Gram-negative rods are a common cause of bacterial infections. Antibiotics are substances produced by certain microorganisms that exhibit bacteriostatic or bactericidal properties. This broader group includes semi-synthetic drugs. There are various classes of antibiotics, including the amphenicol class, which was introduced with the discovery of chloramphenicol in 1947. Macrolides represent another prominent class of antibiotics frequently used in medical treatments (Petty and Francis-Floyd 2020). In agricultural disease management, the most widely employed antibiotics include oxytetracycline, trimethoprim, and florfenicol (Alday-Sanz et al. 2012).

Any exposure to antibiotics, whether during treatment or through prolonged subtherapeutic exposure, can select for resistant mutants, enabling their natural development (Nesse and Simm 2018). The rise of antimicrobial resistance (AMR) has compromised the control of common bacterial aquaculture diseases, such as furunculosis (Aeromonas salmonicida) and edwardsiellosis (Edwardsiella tarda). Furthermore, the presence of antimicrobial residues in food has raised significant concerns regarding food safety, public health, and animal health. The primary public health concern associated with antimicrobial residues is the development of antibiotic resistance. Additionally, residues can cause allergies (e.g., penicillin), nephropathy (e.g., gentamicin), carcinogenicity (e.g., sulfamethazine, furazolidone and oxytetracycline), mutagenicity, anaphylactic shock, teratogenicity, disruption of normal intestinal flora and bone marrow depression (Okocha et al. 2018).

To safeguard consumer health, controlling antibiotic use in aquaculture is necessary. The overuse of antimicrobial drugs in aquaculture leads to disease resistance and adverse health consequences for humans. Two primary concerns associated with antibiotic use in aquaculture are the presence of antimicrobial residues in industry-produced products and the spread of AMR. Alternatively, aquatic animal pathogens may develop resistance, rendering treatments ineffective (Milijasevic et al. 2024).

AMR poses a significant threat to global health, as it can transcend geographical and phylogenetic boundaries, facilitating the exchange of resistant genes between human pathogens and animal diseases. Gene flow can occur through various mechanisms. Unlike terrestrial environments, where animals receive injectable antimicrobials, aquatic animals are primarily treated with medicated feed. Nevertheless, this method has limitations. Reduced feed intake by sick animals can compromise treatment efficacy, and unused medicated feed can accumulate in sediments. This accumulation can foster the growth of resistant bacteria, expanding the pool of resistance in aquatic environments. Consequently, exploring alternatives to antibiotics is crucial (Bondad-Reantaso et al. 2023; Elgendy et al. 2024). This comprehensive review seeks to investigate and identify effective antibiotic alternatives for combating pathogens in aquaculture, with a focus on promoting sustainable and environmentally responsible practices.

Controlling fish infections with antibiotics

Antibiotic therapy is a vital tool in the prevention and control of fish infections, particularly when employed prophylactically (Chen et al. 2018; Binh et al. 2018). By incorporating antibiotics into feed formulations, farmers can therapeutically treat and prevent bacterial diseases in both juvenile and adult fish. Additionally, antibiotics provide a defense against illnesses that emerge during the early stages of fish development. While antibiotics can significantly lower morbidity and mortality rates, encouraging the expansion of aquaculture, their continual small-scale use is also driven by economic factors. Farmers perceive antibiotics as a cost-effective measure, as they believe these drugs help minimize production costs, thereby motivating their continued use in aquaculture (Ringø 2020).

Adverse effects of antibiotics

The use of antibiotics in aquaculture is crucial for maintaining fish health, as emphasized by Limbu et al. (2020). However, administering antibiotics to cultured fish can have unintended consequences. Following ingestion, antibiotics are absorbed into the fish's gastrointestinal tract, distributed to various tissues, and can accumulate, exerting their effects. The impact of antibiotics on fish varies depending on factors such as species, growth stage, type, dosage, and mode of action. Consequently, antibiotic-induced effects can significantly influence the productivity and sustainability of fish aquaculture (Ljubojević Pelić et al. 2024; Table 1).

The global misuse and uncontrolled use of antibiotics have escalated, driven by the misconception that they can reduce manufacturing losses and accelerate growth rates, thereby minimizing the spread of harmful pathogens (Muteeb et al. 2023). Thus, the excessive use of antibiotics in animal protein production poses a significant risk to human health (Romero et al. 2012). According to Guardabassi and Kruse (2010), the misuse of antibiotics can facilitate the zoonotic transfer of resistance genes into the human microbiome. This disruption can have far-reaching consequences, including the killing of beneficial microorganisms, weakened immunity, and impaired nutrition. Furthermore, the widespread use of antibiotics in intensive production systems contributes to environmental pollution and chemical accumulation (Kakoolaki et al. 2013; Su et al. 2017; Saxena et al. 2018).

Antimicrobial resistance in aquaculture

The overuse and misuse of antibiotics in aquaculture have accelerated the development of antimicrobial resistance, rendering the treatment of infectious diseases increasingly challenging. The emergence and dissemination of antibiotic-resistant genes pose a significant threat to global health (Bhat et al. 2020). Anti-

Table 1 The adverse effects of antibiotics on fish species

Antibiotics	Exposure method, dosage and duration	Species	Effects	References
Tetracycline	Exposure 0.02, 0.01, 0.1, 100 µg; 120 h	*Danio rerio*	Survival rates remained unchanged, with no significant variations in body length in treated fishes	Qiu et al. (2020)
Cefalexin	Exposure; 1.3, 2.5, 5 and 10 mg; 96h	*Pomatoschistus microps*	No significant differences were observed in total length and weight between the teated and control groups. However, the treated fish showed reduced predatory performance compared to the control group.	Fonte et al. (2016)
Sulfamethoxazole	Dietary; 100 mg kg^{-1} diet; 84 days	*Oreochromis niloticus*	Weight gain was significantly lower in treated fish than in controls	Limbu et al. (2018)
Norfloxacin	Exposure; 0.0001, 0.1, 1.0, 5.0 and 10.0 mg L^{-1}; 34 days	*Cyprinus carpio*	No significant differences in survival rates	Charvatova et al. (2015)
Florfenicol	Dietary; 20 g; 28 days	*Ctenopharyngodon idella*	Disrupt both luminal and mucosal microbiota	Sun et al. (2021)
Chloramphenicol	Exposure; 2.5, 5.0 and 10.0 mg L^{-1}; 15 days	*Clarias gariepinus*	Treatment-induced behavioral changes in fish included disorientation, erratic swimming, and hyperactive responses.	Nwani et al. (2014)

microbials can select for antibiotic-resistant bacteria and facilitate the transmission of resistance genes (Liu et al. 2017). Furthermore, the presence of antibiotic residues in aquaculture products poses a health risk to consumers. These residues can persist in the environment due to their stability and resistance to biodegradation, subsequently accumulating in shellfish and fish. Studies have detected antibiotic residues, including sulphonamides, tetracyclines, and macrolides, in farmed fish species such as tilapia (Bortolotte et al. 2021), trout (Adel et al. 2017), and salmon (Miranda et al. 2018) from various countries (Done and Halden 2015; Almashhadany et al. 2024).

The consumption of aquaculture products contaminated with antibiotic residues can have carcinogenic and teratogenic effects, disrupting the natural intestinal flora in humans and animals. This issue is not limited to specific regions, as studies from Iran (Mahmoudi et al. 2014), India (Swapna et al. 2012), Bangladesh (Hassan et al. 2013), and Nigeria (Olatoye and Basiru 2013) have reported the presence of antibiotic residues in aquaculture products. The economic implications of antimicrobial resistance in aquaculture are substantial. Notably, the US and EU have rejected a considerable proportion of imported aquaculture products due to antibiotic residues, with rejection rates reaching 20% and 28%, respectively (FAO 2020). This highlights the need for sustainable and responsible use of antibiotics in aquaculture to mitigate the risk of antimicrobial resistance.

Mechanisms of horizontal gene transfer across bacteria to acquire antibiotic resistance

Antibiotic-resistant bacterial strains are rapidly emerging, posing a substantial risk to global health and wellbeing. Research reveals that bacteria can develop resistance to antibiotics through various mechanisms, including horizontal gene transfer (HGT) (Chokshi et al. 2019; Murray et al. 2022). HGT is a pivotal process in bacterial evolution, facilitating the exchange of genetic material between cells. HGT enables bacteria to acquire antibiotic resistance genes (ARGs) through conjugation, transduction, and transformation.

During transformation, donor bacteria release DNA fragments containing antibiotic resistance genes (ARGs) into the environment. These fragments can be taken up by recipient bacteria, which then integrate the ARGs into their genomes, enabling the production of resistance-conferring proteins or enzymes. Transduction, mediated by bacteriophages, allows for the transfer of ARGs from donor to recipient bacteria. The recipient bacterium can then integrate these genes into its genome, acquiring antibiotic resistance. Conjugation occurs through direct cell-to-cell contact between donor and recipient bacteria, facilitated by a specialized structure called a pilus. This process enables the transfer of plasmid-borne ARGs from donor to recipient bacteria, where they are integrated into the chromosome (Chen 2022).

Outer membrane vesicles have been identified as a mechanism for HGT, but the majority of HGT events are mediated by mobile genetic elements (MGEs). MGEs comprise a diverse array of genetic entities, including conjugative DNA elements, transposable DNA elements, and bacteriophages (Tokuda and Shintani 2024). Conjugative DNA elements, such as plasmids and integrative and conjugative elements (ICEs), enable direct transfer of genetic material between bacterial cells through conjugation, a process mediated by type IV secretion systems (Delavat et al. 2017). Transposable DNA elements, including transposons and integrons, facilitate intracellular and inter-replicon gene mobility. Transposons can transpose to new genomic locations, whereas integrons capture and integrate gene cassettes, often conferring antibiotic resistance (Tansirichaiya et al. 2022). Bacteriophages, or phages, are bacterial viruses that can transfer genetic material between cells through transduction. During the phage replication cycle, host DNA can be inadvertently packaged into phage particles and transported to new host cells, facilitating HGT (Schneider 2021). These HGT mechanisms play a crucial role in the dissemination of antibiotic resistance among bacterial populations, highlighting the need for effective strategies to combat the spread of resistance.

Different alternatives to antibiotics

The mechanisms and causes mentioned earlier highlight the need for Innovative solutions to combat bacterial infections. Several options have emerged as potential replacements for antibiotics (Figure 1).

Use of probiotics

Probiotics are beneficial microorganisms that, when administered in sufficient amounts, can positively impact the health and well-being of their host (Diwan et al. 2022). Despite debate surrounding their efficacy in aquaculture, probiotics offer a promising alternative to antibiotics in promoting fish health. In aquaculture, physiological stress responses triggered by chemical and physical factors can lead to disease. These factors include handling-related injuries, fish density, temperature, pH, oxygen and CO_2 concentrations, and the presence of organic matter in the water (Verschuere et al. 2000).

Stress and environmental changes can cause immunosuppression, hindering fish growth. Probiotic interventions can help mitigate these effects by promoting a balanced microbial community, enhancing fish resilience to stress and disease (Dawood et al. 2018; Riaz et al. 2024).

Probiotics provide various benefits, including improved development, health, disease resistance, feed utilization, stress response, and overall vigor (Dawood et al. 2016). Their primary functions include boosting the host's immune system, increasing feed utilization, modifying microbial populations, and enhancing the surrounding environment. In aquatic animals, probiotics are particularly important due to the constant interaction between gut microbiota, surroundings, and host activities (Tong et al. 2023; Riaz et al. 2024).

Various microorganisms, including bacteria, yeasts, and algae, have been explored as probiotics in aquaculture (Irianto and Austin 2002; Gheziel et al. 2019). Probiotic supplements and live microbial feed products help stabilize the host's gastrointestinal microbiota, enhancing aquatic species' survival, growth, and overall health (Hai 2015; Figure 2). In fish aquaculture, probiotics play a significant role, offering financial and operational benefits. For example, *Pseudomonas fluorescens* has been investigated as a pro-

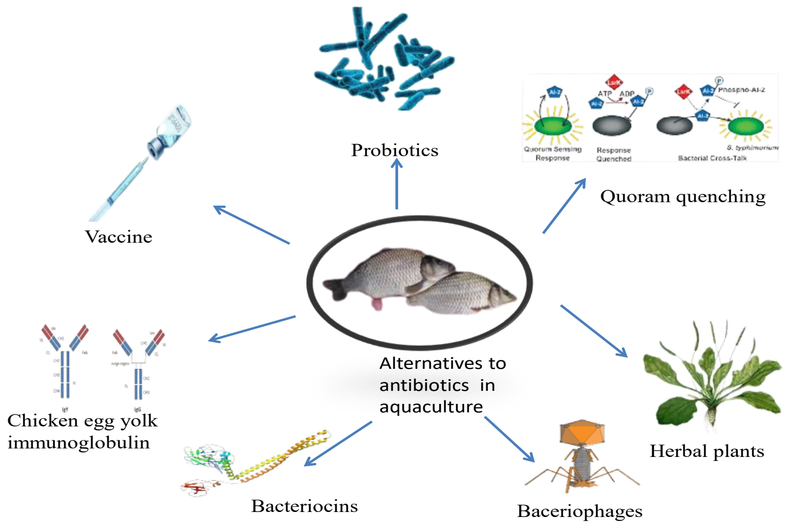

Fig. 1 Some alternatives to antiobiotics

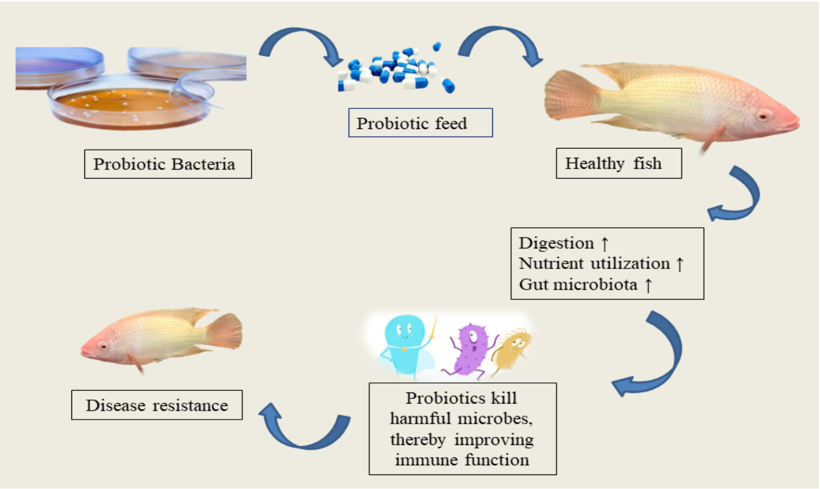

Fig. 2 Probiotics improve disease resistance in aquaculture (Okeke et al. 2022)

biotic agent against two major fish pathogens: *Streptococcus faecium* and *Pseudomonas anguilliseptica*. The latter is a notorious opportunistic pathogen affecting farmed fish globally (Eissa et al. 2014; Table 2).

Mode of action of probiotics

Probiotics exert their role in disease resistance through various mechanisms (Figure 3). They generate various bioactive compounds, including organic acids and antimicrobial substances, which hinder the attachment of harmful bacteria to intestinal binding sites (Tiwari et al. 2012). Additionally, probiotics interact with the host's immune system by regulating immune cells, such as T cells and antigen-presenting cells, to promote a balanced immune response (Oelschlaeger 2010). Furthermore, probiotics alter the phenotype and function of dendritic cells, modulate the NF-kB pathway and AP-1, and control the production of pro-inflammatory cytokines (Roselli et al. 2005). Moreover, they stimulate the production of IgA antibodies, increase natural killer cell activity, and regulate apoptosis and nitric oxide release. They also selectively impact T helper cells and stimulate specific immune cells (Fong et al. 2016).

Use of prebiotics in aquaculture

Prebiotics consist of non-digestible dietary fibers or carbohydrates that foster a favorable gut microbiome by stimulating the growth and activity of beneficial bacteria. By promoting a healthy gut microbiota prebiotics confer benefits to the host's immune system, digestion, and overall well-being. Prebiotics have emerged as a promising strategy to boost disease resistance in aquatic species. By modifying the microbial ecology in the gastrointestinal tract, prebiotics can enhance non-specific immune responses and promote a balanced gut microbiota (Song et al. 2014; Dawood et al. 2016).

Oligosaccharides, a type of prebiotic, selectively ferment, supporting the growth of beneficial anaerobic bacteria while suppressing pathogenic bacteria (Roberfroid 2005). This selective fermentation significantly alters the gut environment, leading to improved immunity and disease resistance (Dawood et al. 2016). Incorporating prebiotics in aquaculture has been shown to increase the production of volatile fatty acids in

Table 2 The effects of probiotics against harmful bacteria in fish

Fish species	Probiotic strains	Bacterial pathogens	Effects	References
Tilapia	*B. licheniformis*	*Streptococcus iniae*	Improved the disease resistance	Han et al. (2015)
Common carp	*Flavobacterium sasangense*	*Aeromonas hydrophila*	Enhance immune response and disease resistance	Chi et al. (2014)
Crucian carp	*Lactobacillus acidophilus*	*Helicobacter pylori*	Upgrade the protein frame of the skin mucus To reduce in fatality rate	Adeshina (2018)
Nile tilapia	*Lactobacillus rhamnosus*	*Pseudomonas fluorescens*	Enhance in hematological parameters, total protein and globulin	Eissa et al. (2014)

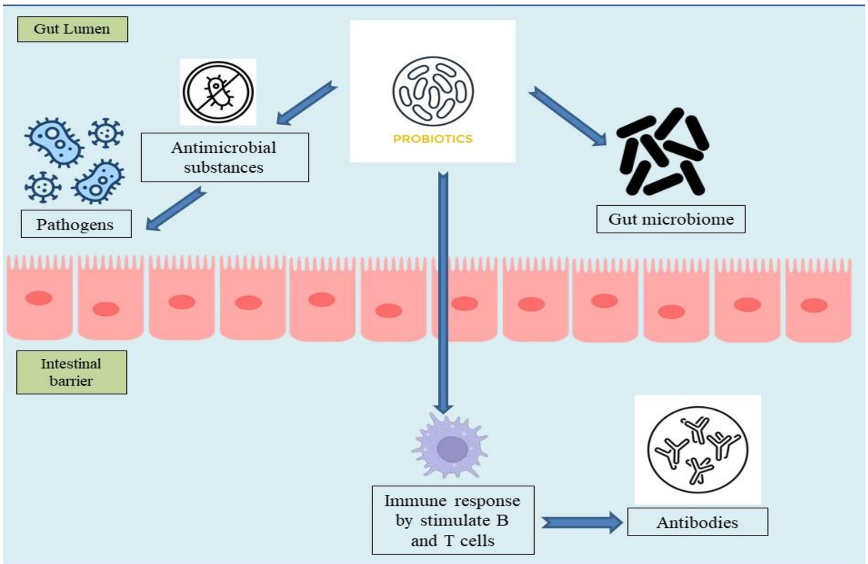

Fig. 3 Mechanism of probiotics as alternatives to antibiotics in combating disease resistance (Zhang et al. 2023)

the GI tract, inhibiting the growth of potentially harmful microorganisms and providing energy to the host (Ganguly et al. 2013). Studies have demonstrated the potential of prebiotics to modulate the gut microbiota and enhance disease resistance in various aquatic species (Patel and Goyal 2012; Iwashita et al. 2022). Further research is necessary to elucidate the mechanisms by which prebiotics exert their beneficial effects and to identify the most effective prebiotic compounds for specific aquatic species.

Organic acids

Organic acids, including citric, lactic, benzoic, and formic acid, are volatile, short-chain fatty acids with antibacterial properties that can improve growth, disease resistance and nutrient utilization in aquatic animals (Ng and Koh 2017). Despite their benefits, research on organic acids in aquaculture is limited, particularly compared to their use in livestock feeds.

Several fish species, such as carp, tilapia, salmon, and rainbow trout, have been the subject of research examining how dietary organic acids influence their growth rates, nutrient uptake, and ability to fight off disease (Reda et al. 2016; Ng and Koh 2017). The findings suggest that organic acids have beneficial effects on aquaculture species, particularly in enhancing disease resistance. The dietary salts of formic acid, such as K-diformate (KDF), have been shown to improve growth, feed utilization, and nutrient digestibility in tilapia (Ramli et al. 2005; Lim et al. 2010; Ng et al. 2009). Furthermore, organic acids have been found to exhibit antibacterial properties, inhibiting the growth of Gram-negative bacteria and modulating gut microbiota (Bai et al. 2015; Ng and Koh 2016). These findings indicate that organic acids have potential as a natural alternative to antibiotics in aquaculture.

Mechanism of action

Organic acids exhibit antibacterial properties by disrupting bacterial cell membranes and releasing protons into the cytoplasm, ultimately inhibiting the growth of Gram-negative bacteria (Bai et al. 2015). To maintain intracellular pH equilibrium, bacteria expend energy (ATP) to extrude protons, leading to cellular energy depletion and eventual death (Defoirdt et al. 2009). The antibacterial mechanism of organic acids involves a multi-step process: disruption of bacterial cell membranes, release of protons into the cytoplasm, inhibition of bacterial growth and depletion of cellular energy (ATP). Notably, organic acids are most effective against bacteria in their undissociated state, particularly at low pH levels (Brul and Coote 1999; Lambert and Stratford 1999; Ng and Koh 2017; Figure 4).

Phytotherapy: Medicinal plants

Phytotherapy, which utilizes compounds derived from medicinal plants for therapeutic purposes, has gained attention in aquaculture. Medicinal herbs have demonstrated broad antiparasitic, antibacterial, and antifungal properties of medicinal herbs in humans and animals (Silva and Fernandes Junior 2010). Herbal rem-

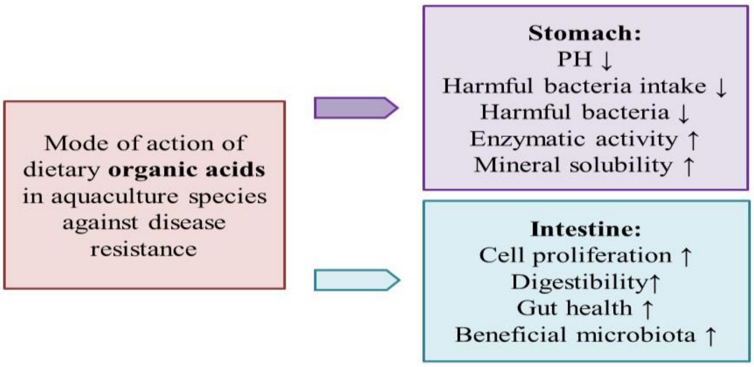

Fig. 4 Mechanism of organic acids as alternatives to antibiotics in combating disease resistance (Bai et al. 2015)

edies have been used for centuries to treat human ailments, and their potential application in aquaculture has only recently been explored (Li et al. 2022). The demand for alternatives to conventional medications, which pose environmental hazards, has driven the development of phytotherapeutic approaches in aquaculture. Strategies for managing and preventing fish infections include the development of prophylactic treatments, such as immunostimulant diets (Skalli et al. 2013). Natural compounds have shown promising preventive effects and improved fish immune responses (Samad et al. 2014; Vaseeharan and Thaya 2014).

To combat pathogen-caused mortality, therapeutic products must be employed during production. Phytotherapeutic ingredients are often administered to fish through water immersion. Medicinal herbs are proposed as a potential substitute for preventing fish disease, given the widespread negative impacts of antimicrobial resistance in aquaculture (Freitas et al. 2020; Iqbal et al. 2024).

Medicinal plants contain antioxidant chemicals that capture free radicals, interfering with regular cell activity (Moreno et al. 2020). Various Asian medicinal plants, such as *Andrographis paniculata, Cinnamon zeylanicum, and Curcuma xanthorrhiza*, have demonstrated efficacy in treating ailments, including metabolic abnormalities and fever (Ismail et al. 2017; Yousaf et al. 2024; Table 3). Herbal medicines contain antibacterial compounds, including proteins, terpenoids, alkaloids, and phenolic compounds, which have shown resistance against bacterial diseases such as *Aeromonas hydrophila, Streptococcus spp Vibrio spp, Edwardsiella ictaluri* (Jafarzadeh et al. 2020; Rodianawati et al. 2015).

Despite their potential, the use of phytotherapeutics in aquaculture feeds to treat parasitic diseases remains understudied. However, their efficacy as a feed additive suggests a promising application in aquaculture. Further research is warranted to explore this mode of administration, particularly against parasites like *Ichthyophthirius multifiliis* that complete part of their life cycle within host tissues (Valladão et al. 2015).

Mechanism of action

Medicinal plants modulate the immune system by targeting the kidneys, spleen, and thymus, enhancing the growth and maturation of immune organs. They stimulate non-specific immunity by activating white blood cells and the monocyte-macrophage system, while also promoting specific immune responses through antibody production. Medicinal plants induce the release of cytokines, including iinterferon, tumour necrosis factor, and interleukin, regulating both non-specific and specific immunity. Their bioactive compounds, such as essential oils, saponins, phenolics, and polysaccharides, exhibit immunopotentiation, antioxidant activity, and stress mediation (Hoseinifar et al. 2020; Anal et al. 2023).

These compounds interact with proteins and DNA, altering their recognition, binding, catalytic activity, and turnover. Phenols and terpenoids in medicinal plants scavenge reactive oxygen species and oxygen free radicals, protecting cells and tissues from oxidative damage (Chong et al. 2020; Figure 5).

Vaccines

Vaccines are mixtures of modified or inactivated pathogens and their metabolites, administered to prevent infectious diseases (Lillehaug et al. 2018). Prophylactic vaccination offers dual benefits: protecting tissues and organs before they become compromised (low pathogen burden) and preventing bacterial growth after initial infection. This proactive approach significantly reduces the likelihood of resistance mutations emerging and spreading. Unlike medications, vaccines contain multiple immunogenic epitopes, making it harder for pathogens to develop resistance (Bagnoli et al. 2017). Consequently, more mutations are required for pathogens to confer resistance against vaccines. Although vaccine resistance can occur, vaccines are less likely to induce it. Vaccines can be administered orally, intramuscularly, intraperitoneally, or through

Table 3 Effects of medicinal plants with antibacterial properties

Pathogen	Host	Active compound	Plants used	References
Aeromonas hydrophila	*Clarias gariepinus*	Allicin	*Allium sativum*	Eirna-Liza et al. (2018)
A. hydrophila	*Labeo rohita*	Sitoindosides	*Indian ginseng*	Sharma et al. (2010)
Miamiensis avidus	*Paralichthys olivaceus*	Saponins	*Herbaceous seepweed*	Harikrishnan et al. (2012)
Edwardsiella ictaluri	*Ctenopharyngodon idella*	Alkaloids; (berberine)	*Berberis aristata*	Ji et al. (2012)
Ichthyophthirius multifiliis	*Ictalurus punctatus*	Pentagalloylglucose	*Galla chinensis*	Valladão et al. (2015)
A. hydrophila	*Labeo rohita, Cirrhinus mrigala, Catla catla*	Terpenoids	*Andrographis paniculate*	Basha et al. (2013)
Staphylococcus aureus	*Salmo trutta*	Menthol	*Mentha piperita*	Adel et al. (2015)

water-based solutions. Injectable vaccinations are crucial for preventing disease in salmon and trout, while water-based vaccinations have been effective against diseases like *Listonella anguillarum* and *Vibrio salmonicida* (Bondad-Reantaso et al. 2023).

The salmonid vaccine industry emerged in the late 1980s with water-based vaccinations. Oil-based vaccinations introduced in the 1990s reduced furunculosis outbreaks (Duff 1942). Today, vaccinations are available for over 22 bacterial infections and six viral diseases in more than 17 fish species, with availability in over 40 countries. However, large-scale industrial vaccination is not widely practiced in major fish-producing nations like China, which accounts for 61% of the world's aquaculture production (Bondad-Reantaso et al. 2023).

Mode of a vaccine action against facultative intracellular bacteria

Immunity against pathogens is typically acquired through two mechanisms: antibodies and cell-mediated immunity (Figure 6). However, antibodies are less effective against intracellular and facultatively intracellular bacteria, such as *Salmonella sp., Listeria monocytogenes*, and *Mycobacterium sp*., which can evade antibody detection by multiplying inside host cells. Although these pathogens can evade antibodies, most

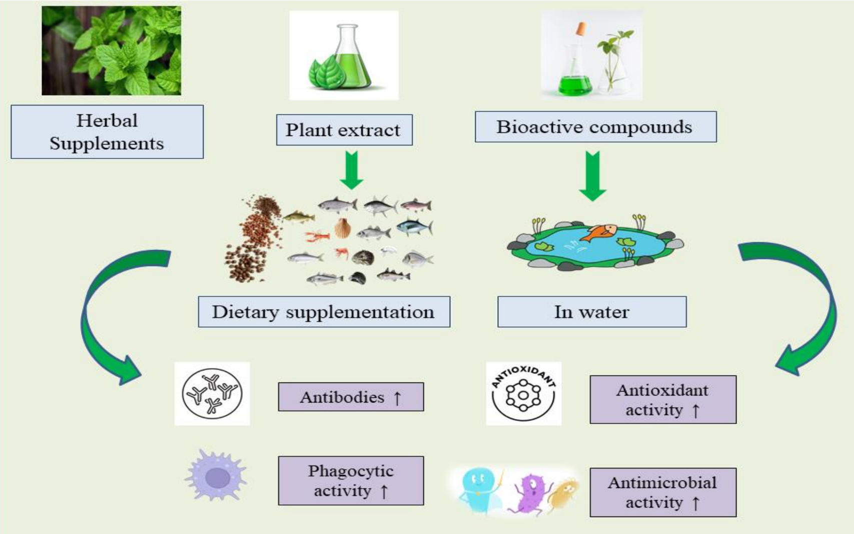

Fig. 5 Mechanism of medicinal plants as alternatives to antibiotics in combating disease resistance (Elgendy et al. 2024)

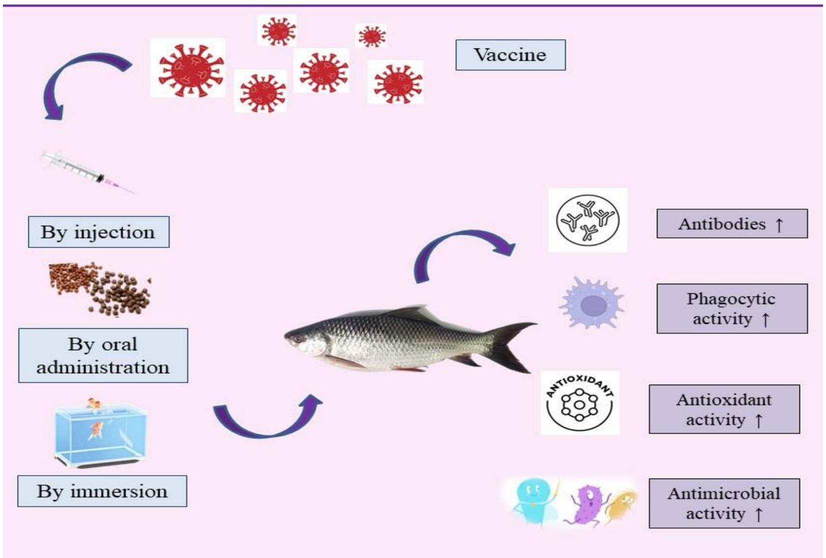

Fig. 6 Mechanism of vaccine as alternatives to antibiotics in combating disease resistance (Bondad-Reantaso et al. 2023)

intracellular pathogens spend part of their infectious cycle in the extracellular space, where they are vulnerable to antibody activity (Haesebrouck et al. 2004; Pridgeon and Klesius 2012).

Cell-mediated immune responses, mediated by Th1-produced lymphokines stimulate cytotoxic T-lymphocytes, which activate macrophages. This activation enhances the ability of macrophages to eliminate facultatively intracellular bacteria. Cytotoxic T-lymphocytes destroy infected host cells, releasing bacteria into the extracellular space where they can be eliminated. Live-attenuated vaccines are generally more effective against facultatively intracellular bacteria, such as *Salmonella sp.,* due to their ability to induce cell-mediated immunity. However, research suggests that inactivated vaccines can also elicit cell-mediated immunity, depending on the adjuvant used (Mondal and Thomas 2022).

Reverse vaccinology

Reverse vaccinology has transformed the vaccine development landscape by harnessing the power of computational genomics and bioinformatics to pinpoint promising vaccine targets within pathogen genomes. This approach identifies specific protein regions (epitopes) that trigger strong immune responses, enabling the creation of multi-epitope vaccines. The benefits of reverse vaccinology include targeting multiple epitopes simultaneously to enhance vaccine efficacy against rapidly evolving antibiotic-resistant bacterial strains, and faster and more precise vaccine development that can potentially overcome the limitations of traditional methods. As antibiotic resistant bacteria remains a pressing global health concern (Enayatkhani et al. 2021; Herrera 2021; Tobuse et al. 2022), reverse vaccinology offers a promising solution for developing effective vaccines. Ongoing research is exploring the application of reverse vaccinology in aquaculture, focusing on developing effective vaccines against major bacterial pathogens such as *Vibrio sp*., *Aeromonas sp*., and *Streptococcus sp* (Mondal and Thomas 2022).

Bacteriophages

Phages or bacteriophages, are viruses that target bacteria, making them harmless to humans. They are among the most abundant viruses, with estimates suggesting approximately 10^31 phages in the biosphere. Phages comprise ten distinct groups, including sessile and tailed phages, each with unique structures.(Abedon et al. 2011). As obligatory bacterial parasites, phages possess a complete genetic makeup, enabling them to multiply within suitable hosts. However, they lack ribosomes and energy-producing machinery, relying on host cells for protein synthesis.

Phage therapy, a medical treatment alternative to antibiotics, has been extensively explored since the

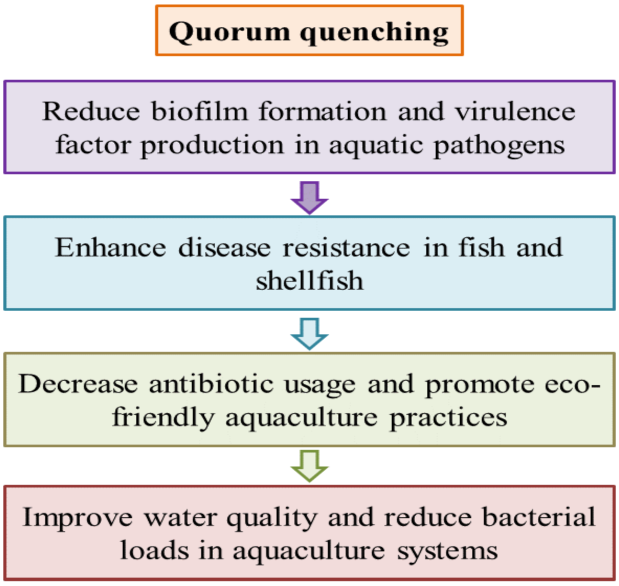

Fig. 7 Quorum quenching in combating disease resistance (Bondad-Reantaso et al. 2023)

discovery of phages in 1915 (Dhama et al. 2013; Tiwari et al. 2014). In aquaculture, phages offer a viable treatment option for bacterial infections due to their specificity, rapid generation time, and minimal environmental impact (Rong et al. 2014; Jamal et al. 2015).

The advantages of phage therapy include its effectiveness against mucosal and topical infections, specificity to particular bacterial populations, and excellent tolerance in therapy. The presence of phages in the human microbiome further contributes to their therapeutic potential. Phage technology has emerged as a promising substitute for antibiotics in medicine, agriculture, and related fields (Weber-Dąbrowska et al. 2016).

Quorum quenching

Quorum quenching (QQ) disrupts the quorum sensing (QS) system, which enables bacteria to synchronize behaviors such as biofilm production, pathogenicity, and light emission (Dong et al. 2001). QS relies on autoinducers, including Acyl-Homoserine Lactones (AHLs), to activate genes in response to population density and species composition (Bondad-Reantaso et al. 2023).

Certain substances can disrupt AHL-mediated QS by degrading AHLs, inhibiting their synthesis, or blocking their interaction with receptors. This disruption prevents harmful bacteria from forming biofilms, producing virulence factors, and reduces their pathogenicity. The potential of QQ to halt gene expression regulating disease progression, virulence, and microbial interactions has attracted considerable research attention (Reen et al. 2018; Figure 7).

QQ has significant potential in aquaculture to prevent bacterial infections and promote sustainable practices. SShaheer et al. (2021) explored the use of AHL-degrading Bacillus spp. as a viable substitute for antibiotics in preventing luminescent vibriosis in shrimp hatcheries. This innovative bio-therapeutic approach offers a promising solution for disease management in shrimp aquaculture.

Conclusion

In conclusion, a multifaceted approach is necessary to address antibiotic resistance, incorporating therapies to minimize antibiotic use. A combination of general and specific strategies is necessary to prevent and treat infections. Effective alternatives include immunotherapeutics, vaccinations, probiotics, and herbal plant-based interventions. Recent biotechnology innovations have enabled the development of novel therapies against aquaculture pathogens. Bio-based and immunoprophylaxis approaches, such as phytotherapeutics and phage therapy, show promise in preventing and treating diseases in aquaculture. TTo promote the ethical and sustainable implementation of these therapies, further research is necessary to evaluate their efficacy, cost implications, and environmental impact. Collaboration among scientists, researchers, and regulatory bodies is crucial for refining these alternative approaches and promoting a healthier and more sustainable aquaculture industry.

Acknowledgments The authors gratefully acknowledge the contributions and assistance of the entire team at the Fish Nutrition Laboratory, GCUF, Pakistan.

Conflict of interest The authors report no conflict of interest.

Data availability statement Data will be made available on request.

References

Abedon ST, Kuhl SJ, Blasdel BG, Kutter, EM (2011) Phage treatment of human infections. Bacteriophage 1(2):66-85. https://doi.org/10.4161/bact.1.2.15845

Adel M, Dadar M, Oliveri Conti G (2017) Antibiotics and malachite green residues in farmed rainbow trout (*Oncorhynchus mykiss*) from the Iranian markets: a risk assessment. Inter J Food Proper 20(2):402-408. https://doi.org/10.1080/10942912.2016.1163577

Adel M, Safari R, Pourgholam R, Zorriehzahra J, Esteban MÁ (2015) Dietary peppermint (*Mentha piperita*) extracts promote growth performance and increase the main humoral immune parameters (both at mucosal and systemic level) of Caspian brown trout (*Salmo trutta* caspius Kessler 1877). Fish Shellfish Immunol 47(1):623-629. https://doi.org/10.1016/j.fsi.2015.10.005

Adeshina I (2018) The effect of *Lactobacillus acidophilus* as a dietary supplement on nonspecific immune response and disease resistance in juvenile common carp, *Cyprinos carpio*. Inter Food Res J 25(6):2345-2351. https://doi.org/10.1007/s10695-020-00796-7

Alday-Sanz V, Corsin F, Irde E, Bondad-Reantaso MG (2012) Survey on the use of veterinary medicines in aquaculture. Improving biosecurity through prudent and responsible use of veterinary medicines in aquatic food production 547:29-44

Almashhadany DA, Hassan AA, Rashid RF, Abdulmawjood A, Khan IU (2024) Assessment and assay comparison for detection of antimicrobial residues in Freshwater Aquaculture Fish in Erbil Governorate, Iraq. Antibiotics 13(3):225. https://doi.org/10.3390/antibiotics13030225

Anal AK, Koirala S, Karna A, Umar M, Thapa SP (2023) Immunomodulation and enhancing the immunity: unveiling the potential of designer diets. Future Foods 100246. https://doi.org/10.1016/j.fufo.2023.100246

Bagnoli F, Payne DJ (2017) Reaction: alternative modalities to address antibiotic-resistant pathogens. Chem 3:369–372. https://doi.org/10.1093/benz/9780199773787.article.b00010044

Bai SC, Katya K, Yun H (2015) Additives in aquafeed: An overview. Feed Feeding Practices Aquac 171-202. https://doi.org/10.1016/B978-0-08-100506-4.00007-6

Basha KA, Ramanm RP, Prasad KP, Kumar K, Nilavan E, Kumar S (2013) Effect of dietary supplemented andrographolide on growth, non-specific immune parameters and resistance against *Aeromonas hydrophila* in *Labeo rohita* (Hamilton). Fish Shellfish Immunol 35(5):1433-1441. https://doi.org/10.1016/j.fsi.2013.08.005

Bhat RAH, Thakuria D, Pant V, Khangembam VC, Tandel RS, Shahi N, Krishna G (2020) Antibacterial and antioomycete activities of a novel designed RY12WY peptide against fish pathogens. Microb Pathogen 149:104591. https://doi.org/10.1016/j.micpath.2020.104591

Binh VN, Dang N, Anh NTK, Thai PK (2018) Antibiotics in the aquatic environment of Vietnam: sources, concentrations, risk and control strategy. Chemosphere 197:438-450. https://doi.org/10.9734/bjpr/2016/23005

Bondad-Reantaso MG, MacKinnon B, Karunasagar I, Fridman S, Alday-Sanz V, Brun E, Caputo A (2023) Review of alternatives to antibiotic use in aquaculture. Rev Aquac 15(4):1421-1451. DOI: 10.1111/raq.12786

Bondad-Reantaso MG, Subasinghe RP, Arthur JR, Ogawa K, Chinabut S, Adlard R, Shariff M (2005) Disease and health management in Asian aquaculture. Veter Parasitol 132(3-4):249-272. https://doi.org/10.1016/j.vetpar.2005.07.005

Bortolotte AR, Daniel D, Reyes FGR (2021) Occurrence of antimicrobial residues in tilapia (*Oreochromis niloticus*) fillets produced in Brazil and available at the retail market. Food Res Intern 140:109865. https://doi.org/10.1016/j.foodres.2020.109865

Brul S, Coote P (1999) Preservative agents in foods: mode of action and microbial resistance mechanisms. Int J Food Microbiol 50(1-2):1-17. https://doi.org/10.1136/bmj.l1497

Charvatova N, Zelinska G, Dobsikova R, Stancova V, Zivna D, Plhalova L, Svobodova Z (2015) The effect of the fluoroquinolone norfloxacin on somatic indices and oxidative stress parameters in early stages of common carp (*Cyprinus carpio* L.). Neuroendocrinol Letters 36:79-87

Chen B, Lin L, Fang L, Yang Y, Chen E, Yuan K, Luan T (2018) Complex pollution of antibiotic resistance genes due to beta-lactam and aminoglycoside use in aquaculture farming. Water Res 134:200-208. https://doi.org/10.1109/edms.1994.771227

Chen W (2022) Will the mRNA vaccine platform be the panacea for the development of vaccines against antimicrobial resistant (AMR) pathogens? Expert Rev Vaccines 21(2):155-157. https://doi.org/10.4103/0974-777x.52974

Chi C, Jiang B, Yu XB, Liu TQ, Xia L, Wang GX (2014) Effects of three strains of intestinal autochthonous bacteria and their extracellular products on the immune response and disease resistance of common carp, *Cyprinus carpio*. Fish Shellfish Immunol 36(1):9-18. https://doi.org/10.1016/j.fsi.2013.10.003

Chokshi A, Sifri Z, Cennimo D, Horng H (2019) Global contributors to antibiotic resistance. J Global Infec Diseases 11(1):36-42. https://doi.org/10.4103/jgid.jgid_110_18

Chong CM, Murthy AG, Choy CY, Lai KS (2020) Phytotherapy in aquaculture: Integration of endogenous application with science. J Environ Biol 41:1204-1214. https://doi.org/10.1108/03055720710838524

Dawood MA, Koshio S, Esteban MÁ (2018) Beneficial roles of feed additives as immunostimulants in aquaculture: a review. Rev Aquac 10(4):950-974. https://doi.org/10.1111/raq.12209

Dawood MA, Koshio S, Ishikawa M, Yokoyama S, El Basuini MF, Hossain MS, Moss AS (2016) Effects of dietary supplementation of *Lactobacillus rhamnosus* or/and *Lactococcus lactis* on the growth, gut microbiota and immune responses of red sea bream, *Pagrus major*. Fish Shellfish Immunol 49:275-285 https://doi.org/10.1016/j.fsi.2015.12.047

Defoirdt T, Boon N, Sorgeloos P, Verstraete W, Bossier P (2009) Short-chain fatty acids and poly-β-hydroxyalkanoates:(New) Biocontrol agents for a sustainable animal production. Biotechnol Adv 27(6):680-685. https://doi.org/10.1016/j.tibtech.2007.08.001

Delavat F, Miyazaki R, Carraro N, Pradervand N, van der Meer JR (2017) The hidden life of integrative and conjugative elements. FEMS Microbiol Rev 41(4):512-537. doi: 10.1093/femsre/fux008

Dhama K, Chakraborty S, Wani MY, Verma AK, Deb R, Tiwari R, Kapoor S (2013) Novel and emerging therapies safeguarding health of humans and their companion animals: a review. Pak J Biol Sci 16(3):101-111. https://doi.org/10.4236/abb.2013.44a008

Diwan AD, Harke SN, Gopalkrishna S, Panche AN (2022) Aquaculture industry prospective from gut microbiome of fish and shellfish: an overview. Anim Physiol Anim Nutr 106:441–469. doi: 10.1111/jpn.13619

Done HY, Halden RU (2015) Reconnaissance of 47 antibiotics and associated microbial risks in seafood sold in the United States. J Hazard Mater 282:10-17. http://dx.doi.org/10.1016/j.jhazmat.2014.08.075

Dong YH, Wang LH, Xu JL, Zhang HB, Zhang XF, Zhang LH (2001) Quenching quorum-sensing-dependent bacterial infection by an N-acyl homoserine lactonase. Nutr 411(6839):813-817. https://doi.org/10.1038/35081101

Duff DCB (1942) The oral immunization of trout against *Bacterium salmonicida*. J Immunol 44(1):87-94

Eirna-Liza N, Hassim HA, Min CC, Syukri F, Karim M (2018) The duration of protection conferred by garlic on African catfish (*Clarias gariepinus*) against *Aeromonas hydrophila*. J Aquac Res Dev 9(552):2. https://doi.org/10.4172/2155-9546.1000552

Eissa N, Abou El-Gheit N, Shaheen AA (2014) Protective effect of *Pseudomonas fluorescens* as a probiotic in controlling fish pathogens. American J BioSci 2(5):175-181. doi: 10.11648/j.ajbio.20140205.12

Elgendy MY, Ali SE, Dayem AA (2024) Alternative therapies recently applied in controlling farmed fish diseases: mechanisms, challenges and prospects. Aquac Inter 32:9017–9078. https://doi.org/10.1007/s10499-024-01603-3

Enayatkhani M, Hasaniazad M, Faezi S, Gouklan H, Davoodian P, Ahmadi N, Ahmadi K (2021) Reverse vaccinology approach to design a novel multi-epitope vaccine candidate against COVID-19: an in silico study. J Biomolecul Struc Dynamics 39(8):2857-2872. https://doi.org/10.4103/jgid.jgid_125_17

FAO (2020) http://www.fao.org/antimicrobialresistance/background/what-is-it/en/ Accessed on 10.09.2022

FAO (2019) Fishery and aquaculture statistics. Global production by production source 1950-2017 (FishstatJ). FAO Fisheries and Aquaculture Department

Fong FLY, Shah NP, Kirjavainen P, El-Nezami H (2016) Mechanism of action of probiotic bacteria on intestinal and systemic immunities and antigen-presenting cells. Int Rev Immunol 35(3):179-188. https://doi.org/10.3109/08830185.2015.1096937

Fonte E, Ferreira P, Guilhermino L (2016) Temperature rise and microplastics interact with the toxicity of the antibiotic cefalexin to juveniles of the common goby (*Pomatoschistus microps*): post-exposure predatory behaviour, acetylcholinesterase activity and lipid peroxidation. Aqua Toxicol 180:173-185. https://doi.org/10.11606/d.76.2018.tde-21062018-152750

Freitas J, Vaz-Pires P, Câmara JS (2020) From aquaculture production to consumption: Freshness, safety, traceability and authentication, the four pillars of quality. Aquac 518:734857. https://doi.org/10.1016/j.aquaculture.2019.734857

Ganguly S, Dora KC, Sarkar S, Chowdhury S (2013) Supplementation of prebiotics in fish feed: a review. Rev Fish Biol Fish 23:195-199. https://doi.org/10.1007/s11160-012-9291-5

Gheziel C, Russo P, Arena MP, Spano G, Ouzari HI, Kheroua O, Capozzi V (2019) Evaluating the probiotic potential of Lactobacillus plantarum strains from Algerian infant feces: towards the design of probiotic starter cultures tailored for developing countries. Probiotics Antimicrob Proteins 11:113-123. https://doi.org/10.1007/s12602-018-9396-9

Guardabassi L, Kruse H (2010) Princípios da utilização prudente e racional de antimicrobianos em animais. Guia de Antimicrob em Veter 17-30. https://doi.org/10.1093/benz/9780199773787.article.b00080150

Haesebrouck F, Pasmans F, Chiers K, Maes D, Ducatelle R, Decostere A (2004) Efficacy of vaccines against bacterial diseases in swine: what can we expect? Veter Microbiol 100(3-4):255-268. https://doi.org/10.21825/vdt.87525

Hai NV (2015) The use of probiotics in aquaculture. J Appl Microbiol 119(4):917-935. https://doi.org/10.1111/jam.12886

Han B, Long WQ, He JY, Liu YJ, Si YQ, Tian LX (2015) Effects of dietary Bacillus licheniformis on growth performance, immunological parameters, intestinal morphology and resistance of juvenile Nile tilapia (*Oreochromis niloticus*) to challenge infections. Fish Shellfish Immunol 46(2):225-231. https://doi.org/10.1016/j.fsi.2015.06.018

Harikrishnan R, Kim JS, Kim MC, Dharaneedharan S, Kim DH, Hong SH, Heo MS (2012) Effect of dietary supplementation with Suaeda maritima on blood physiology, innate immune response, and disease resistance in olive flounder against Miamiensis avidus. Experimen Parasitol 131(2):195-203. https://doi.org/10.1088/1475-7516/2010/05/005

Hassan MN, Rahman M, Hossain MB, Hossain MM, Mendes R, Nowsad AAKM (2013) Monitoring the presence of chloramphenicol and nitrofuran metabolites in cultured prawn, shrimp and feed in the Southwest coastal region of Bangladesh. Egyptian J Aquatic Res 39(1):51-58. https://doi.org/10.1016/j.ejar.2013.04.004

Herrera LRM (2021) Reverse vaccinology approach in constructing a multi-epitope vaccine against cancer-testis antigens expressed in non-small cell lung cancer. Asian Pacific J Cancer Prevention 22(5):1495. https://doi.org/10.31557/apjcp.2021.22.5.1495

Hoseinifar SH, Sun YZ, Zhou Z, Van Doan H, Davies SJ, Harikrishnan R (2020) Boosting immune function and disease bio-control through environment-friendly and sustainable approaches in finfish aquaculture: herbal therapy scenarios. Rev Fish Sci Aquac 28(3):303-321. https://doi.org/10.1080/23308249.2020.1731420

Iqbal T, Salma U, Umair M, Iqbal H, Khalid T, Hyder S (2024) Utilizing medicinal plants for disease treatment in aquaculture: An approach to improve fish health: Medicinal Plants in Aquaculture. MARKHOR The J Zool 03-10. https://doi.org/10.54393/mjz.v5i03.119

Irianto A, Austin B (2002) Probiotics in aquaculture. J Fish Diseases 25(11):633-642. https://doi.org/10.1201/9781315371399-19

Ismail HF, Hashim Z, Soon WT, Ab Rahman NS, Zainudin AN, Majid FAA (2017) Comparative study of herbal plants on the phenolic and flavonoid content, antioxidant activities and toxicity on cells and zebrafish embryo. J Trad Complement Med 7(4):452-465. https://doi.org/10.1016/j.jtcme.2016.12.006

Iwashita MKP, Addo S, Terhune JS (2022) Use of pre-and probiotics in finfish aquaculture. In: Feed Feeding Practices Aquac 269-289. Woodhead Publishing. https://doi.org/10.1016/b978-0-12-821598-2.00002-3

Jafarzadeh S, Jafari SM, Salehabadi A, Nafchi AM, Kumar USU, Khalil HA (2020) Biodegradable green packaging with antimicrobial functions based on the bioactive compounds from tropical plants and their by-products. Trends Food Sci Technol 100:262-277. https://doi.org/10.1016/j.tifs.2020.04.017

Jamal M, Hussain T, Das CR, Andleeb S (2015) Isolation and characterization of a Myoviridae MJ1 bacteriophage against multi-drug resistant *Escherichia coli* 3. Jundishapur J Microbiol 8(11). https://doi.org/10.1201/9781315371399-19

Ji C, Li AH, Gong XN (2012) Effect of berberine hydrochloride on grass carp Ctenopharyngodon idella serum bactericidal activity against Edwardsiella ictaluri. Fish Shellfish Immunol 33(1):143-145. https://doi.org/10.1109/ic2e.2018.00033

Kakoolaki S, Talas ZS, Cakir O, Ciftci O, Ozdemir I (2013) Role of propolis on oxidative stress in fish brain. Basic Clinical Neurosci 4(2):153. PMCID: PMC4202530 PMID: 25337342

Lafferty KD, Harvell CD, Conrad JM, Friedman CS, Kent ML, Kuris AM, Saksida SM (2015) Infectious diseases affect marine fisheries and aquaculture economics. Annual Rev Mar Sci 7:471-496. https://doi.org/10.1146/annurev-marine-010814-015646

Lambert RJ, Stratford M (1999) Weak-acid preservatives: modelling microbial inhibition and response. J Appl Microbiol 86(1):157-164. https://doi.org/10.1093/odnb/9780192683120.013.34384

Li M, Wei D, Huang S, Huang L, Xu F, Yu Q, Li P (2022) Medicinal herbs and phytochemicals to combat pathogens in aquaculture. Aquac Int 30(3):1239-1259. https://doi.org/10.1007/s10499-022-00841-7

Lillehaug A, Børnes C, Grave K (2018) A pharmaco-epidemiological study of antibacterial treatments and bacterial diseases in Norwegian aquaculture from 2011 to 2016. Disease Aqua Organ 128(2):117-125. https://doi.org/10.1016/s2213-2600(21)00181-8

Lim C, Luckstadt C, Klesius P (2010) Use of organic acids, salts in fish diets. Global Aquac Advocate 13(5):45-46. https://doi.org/10.7313/upo9781904761938.009

Limbu SM, Zhang H, Luo Y, Chen LQ, Zhang M, Du ZY (2020) High carbohydrate diet partially protects Nile tilapia (*Oreochromis niloticus*) from oxytetracycline-induced side effects. Environ Pollut 256:113508. https://doi.org/10.1016/j.envpol.2019.113508

Limbu SM, Zhou L, Sun SX, Zhang ML, Du ZY (2018) Chronic exposure to low environmental concentrations and legal aquaculture doses of antibiotics cause systemic adverse effects in Nile tilapia and provoke differential human health risk. Environ Int 115:205-219. https://doi.org/10.1016/j.envint.2018.03.034

Liu S, Fan L, Sun J, Lao X, Zheng H (2017) Computational resources and tools for antimicrobial peptides. J Peptide Sci 23(1):4-12. https://doi.org/10.1002/psc.2947

Ljubojević Pelić D, Radosavljević V, Pelić M, Živkov Baloš M, Puvača N, Jug-Dujaković J, Gavrilović A (2024) Antibiotic residues in cultured fish: Implications for food safety and regulatory concerns. Fishes 9:484. https://doi.org/10.3390/fishes9120484

Mahmoudi R, Gajarbeygi P, Norian R, Farhoodi K (2014) Chloramphenicol, sulfonamide and tetracycline residues in cultured rainbow trout meat (*Oncorhynchus mykiss*). Bulgarian J Veter Medicine 17(2):147-152. https://doi.org/10.2139/ssrn.4419928

Milijasevic M, Veskovic-Moracanin S, Milijasevic JB, Petrovic J, Nastasijevic I (2024) Antimicrobial resistance in aquaculture: Risk mitigation within the one health context. Foods 13(15):2448. https://doi.org/10.3390/foods13152448

Miranda CD, Godoy FA, Lee MR (2018) Current status of the use of antibiotics and the antimicrobial resistance in the Chilean salmon farms. Frontiers Microbiol 9:1284. doi: 10.3389/fmicb.2018.01284

Mondal H, Thomas J (2022) A review on the recent advances and application of vaccines against fish pathogens in aquaculture. Aquac Int 30(4):1971-2000. https://doi.org/10.1007/s10499-022-00884-w

Moreno MA, Zampini IC, Isla MI (2020) Antifungal, anti-inflammatory and antioxidant activity of bi-herbal mixtures with medicinal plants from Argentinean highlands. J Ethnopharmacol 253:112642. https://doi.org/10.1016/j.micres.2010.11.006

Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Aguilar GR, Gray A, Tasak N (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 399(10325):629-655. https://doi.org/10.3325/cmj.2023.64.272

Muteeb G, Rehman MT, Shahwan M, Aatif M (2023) Origin of antibiotics and antibiotic resistance, and their impacts on drug development: A narrative review. Pharmaceuticals 16(11):1615. https://doi.org/10.3390/ph16111615

Nesse LL, Simm R (2018) Biofilm: a hotspot for emerging bacterial genotypes. Adv Applied Microbiol 103:223-246. Academic Press. https://doi.org/10.1093/benz/9780199773787.article.b00129587

Ng WK, Koh CB (2017) The utilization and mode of action of organic acids in the feeds of cultured aquatic animals. Rev Aquac 9(4):342-368. https://doi.org/10.1111/raq.12141

Ng WK, Koh CB, Sudesh K, Siti-Zahrah A (2009) Effects of dietary organic acids on growth, nutrient digestibility and gut microflora of red hybrid tilapia, *Oreochromis* sp., and subsequent survival during a challenge test with *Streptococcus agalactiae*. Aquac Res 40(13):1490-1500. https://doi.org/10.1111/j.1365-2109.2009.02249.x

Nwani CD, Mkpadobi BN, Onyishi G, Echi PC, Chukwuka CO, Oluah SN, Ivoke N (2014) Changes in behavior and hematological parameters of freshwater African catfish *Clarias gariepinus* (Burchell 1822) following sublethal exposure to chloramphenicol. Drug Chemical Toxicol 37(1):07-113. https://doi.org/10.3109/01480545.2013.834348

Oelschlaeger TA (2010) Mechanisms of probiotic actions–a review. Int J Med Microbiol 300(1):57-62. https://doi.org/10.1016/j.ijmm.2009.08.005

Okeke ES, Chukwudozie KI, Nyaruaba R, Ita RE, Oladipo A, Ejeromedoghene O, Okoye CO (2022) Antibiotic resistance in aquaculture and aquatic organisms: a review of current nanotechnology applications for sustainable management. Environ Sci Poll Res 29(46):69241-69274. https://doi.org/10.1007/s11356-022-22319-y

Okocha RC, Olatoye IO, Adedeji OB (2018) Food safety impacts of antimicrobial use and their residues in aquaculture. Public Health Rev 39:1-22. https://doi.org/10.1016/j.aquaculture.2020.736195

Olatoye IO, Basiru A (2013) Antibiotic usage and oxytetracycline residue in African catfish (*Clarias gariepinus* in Ibadan, Nigeria). World Fish Mar Sci 5(3):302-309. https://doi.org/10.2478/hssr-2018-0014

Patel S, Goyal A (2012) The current trends and future perspectives of prebiotics research: a review. Biotech 2:115– 125. https://doi.org/10.1007/s13205-012-0044-x

Petty BD, Francis-Floyd R (2020) Bacterial diseases of fish. Merck veterinarymanual. Merck and Co., Inc. Retrieved from https://www.msdvetmanual.com/exotic-and-laboratory-animals/aquarium-fish/bacterial-diseases-of-fish

Pradeepkiran JA (2019) Aquaculture role in global food security with nutritional value: a review. Trans Anim Sci 3(2):903-910. https://doi.org/10.1093/tas/txz012

Pridgeon JW, Klesius PH (2012) Major bacterial diseases in aquaculture and their vaccine development. CABI Rev (2012):1-16. https://doi.org/10.1079/PAVSNNR20127048

Qiu W, Liu X, Yang F, Li R, Xiong Y, Fu C, Zheng C (2020) Single and joint toxic effects of four antibiotics on some metabolic pathways of zebrafish (*Danio rerio*) larvae. Sci Total Environ 716:137062. https://doi.org/10.1016/j.scitotenv.2020.137062

Ramli N, Heindl U, Sunanto S (2005) Effect of potassium-diformate on growth performance of tilapia challenged with *Vibrio anguillarum*. In world aquac society conference. Abstract, CD-Rom, Bali, Indonesia. https://doi.org/10.1093/gao/9781884446054.article.t037258

Reda RM, Mahmoud R, Selim KM, El-Araby IE (2016) Effects of dietary acidifiers on growth, hematology, immune response and disease resistance of Nile tilapia, *Oreochromis niloticus*. Fish Shellfish Immunol 50:255-262. https://doi.org/10.1016/j.fsi.2016.01.040

Reen FJ, Gutiérrez-Barranquero JA, Parages M, O´ Gara F (2018) Coumarin: a novel player in microbial quorum sensing and biofilm formation inhibition. Appl Microbiol Biotechnol 102:2063-2073. https://doi.org/10.1007/s00253-018-8787-x

Riaz D, Hussain SM, Sarker PK, Ali S, Naeem A, Naeem E, Farah MA (2024) Use of protexin as a probiotic-supplemented feed additive: Assessment of growth, digestibility, serum antioxidant enzyme activity, and blood profile in *Cirrhinus mrigala*. Frontiers Sustainable Food Systems 8:1449325. https://doi.org/10.3389/fsufs.2024.1449325

Ringø E (2020) Probiotics in shellfish aquaculture. Aquac Fish 5(1):1-27. https://doi.org/10.1016/j.aaf.2019.12.001

Roberfroid MB (2005) Introducing inulin-type fructans. British J Nutr 93(S1):S13-S25. https://doi.org/10.1079/bjn20041350

Rodianawati I, Hastuti P, Cahyanto MN (2015) Nutmeg's (Myristica fragrans Houtt) oleoresin: effect of heating to chemical compositions and antifungal properties. Procedia Food Sci 3:244-254. https://doi.org/10.1016/j.profoo.2015.01.027

Romero J, Feijoó CG, Navarrete P (2012) Antibiotics in aquaculture–use, abuse and alternatives. Health Environ Aquac 159(1):159-198. https://doi.org/10.1016/j.egyr.2020.11.170

Rong R, Lin H, Wang J, Khan MN, Li M (2014) Reductions of Vibrio parahaemolyticus in oysters after bacteriophage application during depuration. Aquac 418:171-176. https://doi.org/10.1016/j.aquaculture.2013.09.028

Roselli M, Finamore A, Britti MS, Bosi P, Oswald I, Mengheri E (2005) Alternatives to in-feed antibiotics in pigs: Evaluation of probiotics, zinc or organic acids as protective agents for the intestinal mucosa. A comparison of in vitro and in vivo results. Anim Res 54(3):203-218. https://doi.org/10.1051/animres:2005012

Samad APA, Santoso U, Lee MC, Nan FH (2014) Effects of dietary katuk (*Sauropus androgynus* L. Merr.) on growth, non-specific immune and diseases resistance against Vibrio alginolyticus infection in grouper *Epinephelus coioides*. Fish Shellfish Immunol 36(2):582-589. https://doi.org/10.1109/60.849126

Saxena SK, Rangasamy R, Krishnan AA, Singh DP, Uke SP, Malekadi PK, Gupta A (2018) Simultaneous determination of multi-residue and multi-class antibiotics in aquaculture shrimps by UPLC-MS/MS. Food Chem 260:336-343. https://doi.org/10.1016/j.foodchem.2018.04.018

Schneider CL (2021) Bacteriophage-mediated horizontal gene transfer: transduction. Bacteriophages: Biol Technol Therapy 151-192. https://doi.org/10.1007/978-3-319-41986-2_4

Selamoglu Z (2018) Selenium compounds for fish health: An update. J Survey Fish Sci 1-4. DOI: https://doi.org/10.17762/sfs.v4i2.144

Shaheer P, Sreejith VN, Joseph TC, Murugadas V, Lalitha KV (2021) Quorum quenching *Bacillus* spp.: an alternative biocontrol agent for *Vibrio harveyi* infection in aquaculture. Diseases Aqua Organ 146:117-128. doi: 10.3354/dao03619. PMID: 34617517

Sharma A, Deo AD, Riteshkumar ST, Chanu TI, Das A (2010) Effect of *Withania somnifera* (*L. Dunal*) root as a feed additive on immunological parameters and disease resistance to *Aeromonas hydrophila* in *Labeo rohita* (Hamilton) fingerlings. Fish Shellfish Immunol 29(3):508-512. https://doi.org/10.1016/j.fsi.2010.05.005

Silva NCC, Fernandes Júnior AJJOVA (2010) Biological properties of medicinal plants: a review of their antimicrobial activity. J Venom Anim Toxins Trop Diseases 16:402-413. https://doi.org/10.14214/sf.a27494

Skalli A, Castillo M, Andree KB, Tort L, Furones D, Gisbert E (2013) The LPS derived from the cell walls of the Gram-negative bacteria *Pantoea agglomerans* stimulates growth and immune status of rainbow trout (*Oncorhynchus mykiss*) juveniles. Aquac 416:272-279. https://doi.org/10.1016/j.aquaculture.2013.09.037

Song SK, Beck BR, Kim D, Park J, Kim J, Kim, HD, Ringø E (2014) Prebiotics as immunostimulants in aquaculture: a review. Fish Shellfish Immunol 40(1):40-48. https://doi.org/10.1016/j.fsi.2014.06.016

Su H, Liu S, Hu X, Xu X, Xu W, Xu Y, Cao Y (2017) Occurrence and temporal variation of antibiotic resistance genes (ARGs) in shrimp aquaculture: ARGs dissemination from farming source to reared organisms. Sci Total Environ 607:357-366. https://doi.org/10.22541/au.169329258.80997445/v1

Sun BY, Yang HX, He W, Tian DY, Kou HY, Wu K, Song XH (2021) A grass carp model with an antibiotic-disrupted intestinal microbiota. Aquac 541:736790. https://doi.org/10.1016/j.aquaculture.2021.736790

Swapna KM, Rajesh R, Lakshmanan, PT (2012) Incidence of antibiotic residues in farmed shrimps from the southern states of India. NIScPR 344-347. http://nopr.niscpr.res.in/handle/123456789/14549

Tansirichaiya S, Goodman RN, Guo X, Bulgasim I, Samuelsen Ø, Al-Haroni M, Roberts AP (2022) Intracellular transposition and capture of mobile genetic elements following intercellular conjugation of multidrug resistance conjugative plasmids from clinical *Enterobacteriaceae* isolates. Microbiol Spectrum 10(1):02140-21

Tiwari G , Tiwari R, Pandey S, Pandey P (2012) Promising future of probiotics for human health: Current scenario. Chronic Young Scien 3(1):17-17. https://doi.org/10.4103/2229-4708.72223

Tiwari R, Dhama K, Kumar A, Rahal A, Kapoor S (2014) Bacteriophage therapy for safeguarding animal and human health: a review. Pakistan J Biol Sci: PJBS 17(3):301-315. https://doi.org/10.1155/2014/761264

Tobuse AJ, Ang CW, Yeon KY (2022) Modern vaccine development via reverse vaccinology to combat antimicrobial resistance. Life Sci 302:120660. https://doi.org/10.1016/j.lfs.2022.120660

Tokuda M, Shintani M (2024) Microbial evolution through horizontal gene transfer by mobile genetic elements. Microbial Biotechnol 17(1):14408. DOI: 10.1111/1751-7915.14408

Tong DQ, Lu ZJ, Zeng N, Wang XQ, Yan HC, Gao CQ (2023) Dietary supplementation with probiotics increases growth performance, improves the intestinal mucosal barrier and activates the Wnt/β-catenin pathway activity in chicks. J Sci Food Agriculture 103:4649–4659. doi: 10.1002/jsfa.12562

Valladão GMR, Gallani SU, Pilarski F (2015) Phytotherapy as an alternative for treating fish disease. J Veter Pharmacol Therapeu 38(5):417-428. https://doi.org/10.1111/jvp.12202

Vaseeharan B, Thaya R (2014) Medicinal plant derivatives as immunostimulants: an alternative to chemotherapeutics and antibiotics in aquaculture. Aquac Int 22:1079-1091. https://doi.org/10.1201/9781003296621-25

Verschuere L, Rombaut G, Sorgeloos P, Verstraete W (2000) Probiotic bacteria as biological control agents in aquaculture. Microbiol Molecular Biol Rev 64(4):655-671. https://doi.org/10.1128/mmbr.64.4.655-671.2000

Weber-Dąbrowska B, Jończyk-Matysiak E, Żaczek M, Łobocka M, Łusiak-Szelachowska M, Górski A (2016) Bacteriophage procurement for therapeutic purposes. Frontiers Microbiol 7:1177. https://doi.org/10.3389/fmicb.2016.01177

Yousaf Z, Hussain SM, Ali S, Sarker PK, Al-Ghanim KA (2024) Recuperative effects of cinnamon (*Cinnamomum zeylanicum*) in *Catla catla* after sub-lethal exposure to lead. Biol Trace Elem Res 1-10. https://doi.org/10.1007/s12011-024-04213-5

Zhang Y, Zhang Y, Liu F, Mao Y, Zhang Y, Zeng H, Yu J (2023) Mechanisms and applications of probiotics in prevention and treatment of swine diseases. Porcine Health Manage 9(1):5. https://doi.org/10.1186/s40813-022-00295-6

Publisher's Note