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REVIEW ARTICLE

Application of Outer Membrane Protein A-based Recombinant Vaccines against Bacterial Fish Pathogens: A Global Perspective on Current Advances, Challenges, and Future Perspectives

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Abstract

Bacterial illnesses remain major issues for the sustainability of aquaculture, causing high mortality rates, reduced growth and efficiency of production, and enormous economic losses globally. The growing use of antibiotics in treating infections has also raised awareness regarding antimicrobial resistance and environmental impact, hence the need for safer and sustainable alternatives. Recombinant subunit vaccines appear to be promising tools in preventing bacterial infections, with a special focus on outer membrane protein A (OmpA) because of its surface exposure, evolutionary conservation, immunogenicity, and its role in bacterial virulence and interactions between pathogens and hosts. This review describes current understanding of OmpA as a potential vaccine candidate. Current evidence of OmpA-based recombinant vaccines against important fish pathogens such as *Edwardsiella tarda*, *Aeromonas hydrophila*, and *Vibrio* species is described, paying attention to the power of these vaccines' stimulation of innate and adaptive immunity against subsequent infection. The paragraph discusses recent advancements in fields such as recombinant protein production, reverse and structural vaccinology, immunoinformatics, multiepitope vaccine creation, and degradable delivery systems such as chitosan and poly(lactic-co-glycolic acid) nanoparticles. Ideas are put forth that need to be worked on since some obstacles remain to achieving the desired results, such as variation in antigenicity among bacterial strains, gaining a thorough understanding of long-term mucosal immunity, a proper method of vaccination that could be universally accepted, producing sufficient amounts of the vaccine, and obtaining adequate practical validation. Future studies have to be conducted focusing on the identification of protective epitopes, improving cross-protective ability, improving delivery systems used for oral and immersion purposes, and carrying out the necessary long-term studies in the field. In general, OmpA is considered to be a good basis for creating next-generation recombinant vaccines that will be aimed at providing assistance in overcoming the problem of dependence on antibiotics and increasing sustainability of aquaculture around the world.

Key words: Antimicrobial resistance, aquaculture, bacterial fish pathogens, fish immunity, immunoinformatics, nanovaccine, outer membrane protein A, recombinant vaccine

INTRODUCTION

Aquaculture is rapidly emerging as one of the most successful players in the food production industry because of its crucial impact on food security, health, and welfare of the population. Progress in breeding, hatchery management, feed technology, disease diagnostics, and farming techniques has made it possible to significantly increase aquaculture production

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of finfish and other aquatic organisms. Aquaculture not only delivers high-quality protein and other necessary nutrients to consumers but also provides livelihoods for millions of people around the globe.[1,2] On the other hand, rapid growth of the aquaculture sector has led to an increase in infectious disease incidence that obstructs sustainable aquaculture production due to massive mortalities, low growth rates, feed efficiency, and the generation of significant economic losses. Among infectious diseases, bacterial diseases are responsible for massive outbreaks in aquaculture, affecting fish farming both in freshwater and seawater. High stocking densities, transportation stress, poor water quality, environmental fluctuations, and climate change can weaken fish immunity and promote pathogen spread. A range of mechanisms for virulence, such as adherence, biofilm formation, toxin production, quorum sensing, iron acquisition, and immune evasion, are utilized by many Gram-negative bacteria such as *Vibrio*, *Aeromonas*, *Edwardsiella*, *Photobacterium*, *Flavobacterium*, and *Yersinia*, along with various Gram-positive bacteria, to infect organisms. Seven causes of disease include septicemia, ulceration, tissue necrosis, and mortality, which cause massive economic damage worldwide. In traditional aquaculture, disease control is achieved through antibiotics, chemotherapeutics, enhanced management, probiotics, immunostimulators, and conventional vaccines.[3-5] Despite the benefits of these methods in controlling disease incidence, the excessive use of antibiotics has led to antimicrobial resistance, environmental contamination, and a series of restrictions that are imposed by authorities. Traditional vaccines, synthetic, live-attenuated, etc., have proven effective but are often hampered by problems such as differences in antigens, cross-protection, concerns related to safety, and issues related to practical implementation of vaccination on a large scale. Recombinant subunit vaccines have shown great promise, as they make use of purified and protective antigens without the need for cultivation of the dangerous viruses. Compared to whole-cell vaccines, recombinant vaccines have increased biosafety, uniform antigen composition, the capability of reproducible production, and possibilities for molecular engineering for improving immunogenic properties.[6-8] With the development of recombinant DNA technology, structural biology, reverse vaccinology, and immunoinformatics, finding appropriate conserved bacterial antigens for vaccine development has become possible. Outer membrane proteins (OMPs) are the most interesting candidates in this chain, due to their accessibility, conservation in Gram-negative bacteria, and their importance in bacterial virulence and interactions with host organisms. Outer membrane protein A (OmpA) is one of the most abundant and highly conserved OMPs in Gram-negative bacteria. Besides serving to maintain the integrity of the membrane, OmpA provides the ability of adhesion, biofilm formation, immunity, adaptation, and survival of the bacteria itself.[9-11] Therefore, this review summarizes all achievements in OmpA research by analyzing OmpA biology, its role in bacterial virulence, new successes in recombinant vaccine development, experiences with leading bacterial pathogens, new methods of vaccine delivery, existing problems, and perspectives for future research.

OVERVIEW OF MAJOR BACTERIAL FISH PATHOGENS

The rapid growth of aquaculture has gone hand in hand with a rise in the number of bacterial diseases, which continue to be one of the most important biological constraints in sustainable fish production. This is because aquaculture has an intensive farming method that uses high stocking density, environmental changes, and water deterioration. All these methods cause physiological stress on the fish, thus impairing their immunity and making it easy for pathogens to spread. The infections that occur result not only in loss of fish life but also ensure that there is a decrease in growth performance, feed efficacy, and loss in yields. The Gram-negative bacterium is among the most economically significant group of fish disease-causing pathogens in aquaculture.[12,13] Some of the members of these genera include *Vibrio, Aeromonas, Edwardsiella, Photobacterium, Flavobacterium, Piscirickettsia,* and *Yersinia, which* cause diseases in fish. Various virulence factors contribute to their pathogenicity, including bacterial adhesion, biofilm formation, toxin and enzyme production, iron uptake mechanisms, cell-to-cell communication, survival in cells, and ability to escape from the immune system. As a result, infected fish are at risk of developing hemorrhagic septicemia, skin ulcers, erosion of fins, exophthalmia, ascites, necrosis of vital organs, granulomatosis, and high rates of mortality. Many pathogens have conserved antigens on their surface, which makes them suitable for the development of vaccines.[14-16] The impact of other pathogens such as *Photobacterium damselae* subsp. piscicida, *Flavobacterium columnare*, *Yersinia ruckeri,* and *Piscirickettsia salmonis* reflects the ongoing threat of pathogenic bacteria in aquaculture. Although Gram-negative bacteria show taxonomic diversity, Gram-negative bacterial pathogens express some OMPs that are conserved, thus contributing to the stability of the cell wall, transport, adhesion, biofilm formation, adaptation in various environmental conditions, and interactions with the host. Since OMPs are exposed on the bacterial surface, they become targets for vaccine development. Of many OMPs, OmpA is the most famous, as it is highly conserved, performs numerous functions in physiology, and can stimulate a protective immune response against different pathogens. Hence, OmpA is viewed by aquaculture as a potential candidate for universal vaccines.[17,18]

BIOLOGY AND STRUCTURAL CHARACTERISTICS OF OMPA

Due to its evolutionary conservation and several functionalities, OmpA is one of the most studied proteins in the family of bacterial OMPs. OmpA is dissimilar from proteins with specialized functions because it plays a role in membrane stability, environmental adaptation, nutrient homeostasis, interaction with hosts, etc. Because of its constitutive expression, OmpA is always present on the bacterial surface, thus making it an attractive antigen for vaccine production. OmpA's structure contains two domains.[19] Based on the characteristics of an ideal antigen for recombinant vaccine purposes, OmpA qualifies as such from the perspective of being surface-exposed, structurally conserved, and functionally significant to bacterial life.[20,21] In addition, the variations in the extracellular loops may still play a role in maintaining the overall architecture of the protein while being important for receptor binding, tropism to specific tissues, and antigenicity, which makes OmpA a good target for rational vaccine development. Genomic comparisons clearly demonstrate that the gene encoding OmpA has been identified in many Gram-negative bacterial species and displays conservation in those parts of the structure that are necessary for correct assembly and stability of its membrane-forming molecules. All recent advancements in structural biology, computational modeling, and immunoinformatics serve to strengthen the potential of OmpA for use as a possible vaccine.[22-24] The high-resolution structural data made possible by structural analyses enabled the identification of conserved congenital B-cell and T-cell epitopes located mostly in the exterior regions of the protein, which aided in implementing reverse vaccinology. The application of computational methods that predict parameters such as antigenicity, structural stability, or immunogenicity facilitated the prompt design of recombinant OmpA vaccines.

STRUCTURAL ORGANIZATION OF OMPA

OmpA can be configured into two domains within its structure, i.e., the transmembrane β-barrel N-terminal domain and periplasmic C-terminal domain. The N-terminal domain includes eight β-barrels which are found inside the outer membrane, attached to the external part of the membrane through loops and turns. The fact that OmpA performs such necessary functions for the cell has created a possibility of its high evolutionary conservation. Results of structural studies show high conservation of the membrane-spanning b-strands and peptidoglycan-binding sites, whereas the sequence of extracellular loops varies significantly. Thus, the information obtained has accelerated reverse vaccinology and the development of multiepitope vaccines and vaccines that utilize nanoparticles as delivery vehicles for antigens, hence providing for reasonable development of modern vaccines based on OmpA for bacterial fish pathogens.[24,25] In summary, the conserved structural feature of OmpA provides molecular grounds for its various physiological roles, surface exposure, and immunogenic properties, which contribute to increasing attention of researchers to this molecule as a vaccine target and illustrate structural principles that allow for understanding of OmpA's role in bacterial adhesion, implantation, immune response, and pathogenicity.

BIOLOGICAL FUNCTIONS OF OMPA

Although initially described as a structural OMP, OmpA is now known as a multipurpose protein that helps maintain outer membrane structure and integrity, preserves cell shape, facilitates the adhesion of cells, contributes to biofilm development, and enables interactions between pathogenic microorganisms and their host. Thus, due to its significant role in bacterial physiology and infection, OmpA has become one of the most common targets of antibacterial approaches and the development of recombinant vaccines. The main function of OmpA is to preserve the integrity of the basic bacterial envelope. Due to the highly conserved C-terminal domain, OmpA links the outer cell membrane to the peptidoglycan layer underneath it, helping stabilize the structure of the bacterial envelope and ensuring its stability and integrity during cell division.[9,26] Experiments indicate that changes made in ompA genes lead to elevated permeability of the cell envelope, abnormal cell structure, and slowed growth rate of bacteria, as well as elevated sensitivity of microbial cells to surrounding stress factors. In fact, all functions performed by OmpA, including membrane stabilization, adhesion, biofilm generation, and its interaction with the immune system, as well as bacterial survival, prove OmpA's importance in the physiology and pathology of Gram-negative bacteria. Overall, owing to its being easily accessible, evolutionarily preserved, and functional, OmpA is regarded as a candidate for creating fish vaccines from its substances.

OMPA AS A VIRULENCE DETERMINANT IN BACTERIAL FISH PATHOGENS

OmpA not only serves a structural purpose, but it also helps in early contact, adherence, colonization, biofilm formation, stability, and immune escape. OmpA is present on the bacterial surface and can be involved in interactions with host tissues from the beginning. One of the key functions of OmpA involved in virulence is ensuring pathogenic adherence. When pathogens can attach to epithelial cells, they can fight against action from physical removal, colonize, and start the infection process, as shown in Figure 1. The behavior of OmpA is associated with other virulence factors such as hemolysins, proteases, secretion

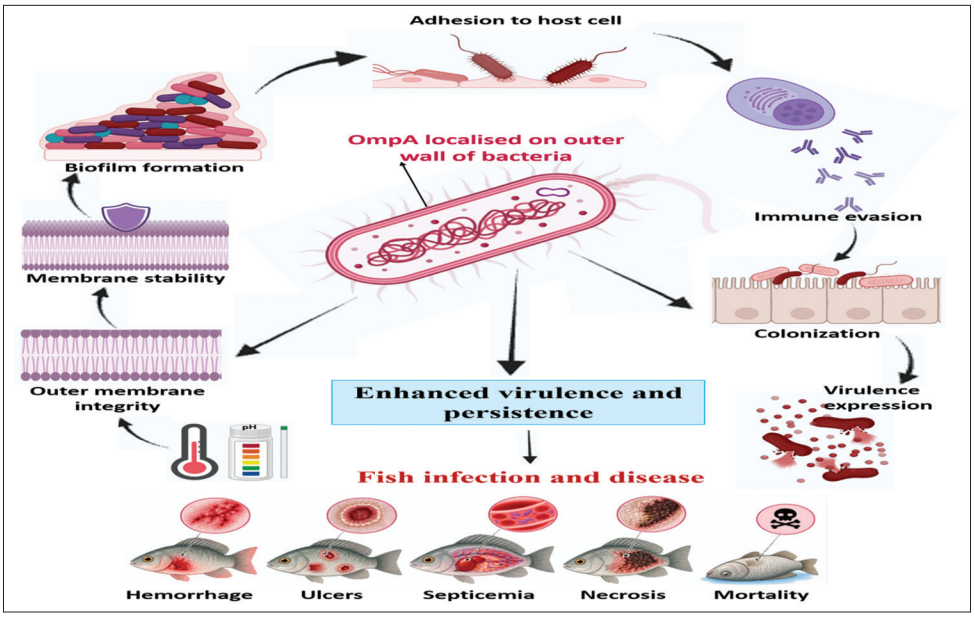


Figure 1: Biological functions and virulence-associated roles of outer membrane protein A in Gram-negative bacterial fish pathogens

systems, adhesins, and quorum-sensing systems governing the abilities of the pathogen to start infection and avoid the body of the host. Even though the role of OmpA may vary from one organism to another, the observations point to its role in bacterial colonization, survival in the body, and development of the disease. Thus, targeting OmpA by recombinant vaccination has a double advantage in that it leads to the protective immune response being activated and the processes that are necessary for bacterial pathogenesis being disrupted.[27]

OMPA AS A RECOMBINANT VACCINE CANDIDATE

Selection of OmpA as a vaccine antigen

Choosing the right antigen is the key step in the development of recombinant subunit vaccines. The ideal antigen is expected to be conserved among different pathogenic strains, exposed to the immune system of the host, able to induce long-term responses, and crucial to bacterial survival or pathogenicity. In the case of Gram-negative bacterial proteins, OMPs meet a major part of these conditions due to their presence on the surface of bacteria and their implication in host–pathogen interactions. OmpA is known to be one of the best examples of vaccine antigens due to its conservation during evolution, multiple functions, and immunogenic properties. OmpA has numerous benefits in comparison to other proteins. Due to its presence on the surface of bacteria, it can be recognized by antibodies produced after vaccination immediately in the course of infection, allowing for blocking the adhesion process. Clinical trials have shown that recombinant OmpA activates innate and adaptive immunity. Vaccinated fish have increased levels of immunoglobulin in blood serum, increased amounts of lysozyme and complement activity, and increased activity of the genes involved in immunity.[28] In the latest developments in science, the processes of structural vaccinology, reverse vaccinology, and immunoinformatics have provided OmpA with new opportunities for being synthesized by identifying the regions of the protein that can trigger immunity. This technology can be combined with DNA synthesis for creating a way of producing vaccines against fish-related diseases. However, the effectiveness of the vaccine will still depend on the design of the antigen involved, its sequence variability, and the type of adjuvant.[29]

Recombinant expression and production of OmpA

Recombinant DNA technology makes it possible to produce purified antigenic protein without having to culture pathogenic bacteria, thus providing better and safer vaccines than conventional bacterins. OmpA is very popular in recombinant protein research related to vaccines in fish due to its availability, conservation, and immunogenic properties. In general terms, recombinant protein production starts with amplifying the OmpA gene by means of PCR, cloning it into the proper vector, and heterologous expression in *Escherichia coli*. Both injectable and oral vaccination options seem feasible with such nanocarriers, as shown in Figure 2. It is crucial to keep optimizing expression systems, protein folding, purification, and formulation in order to create commercially applicable OmpA-based vaccines.[30,31]

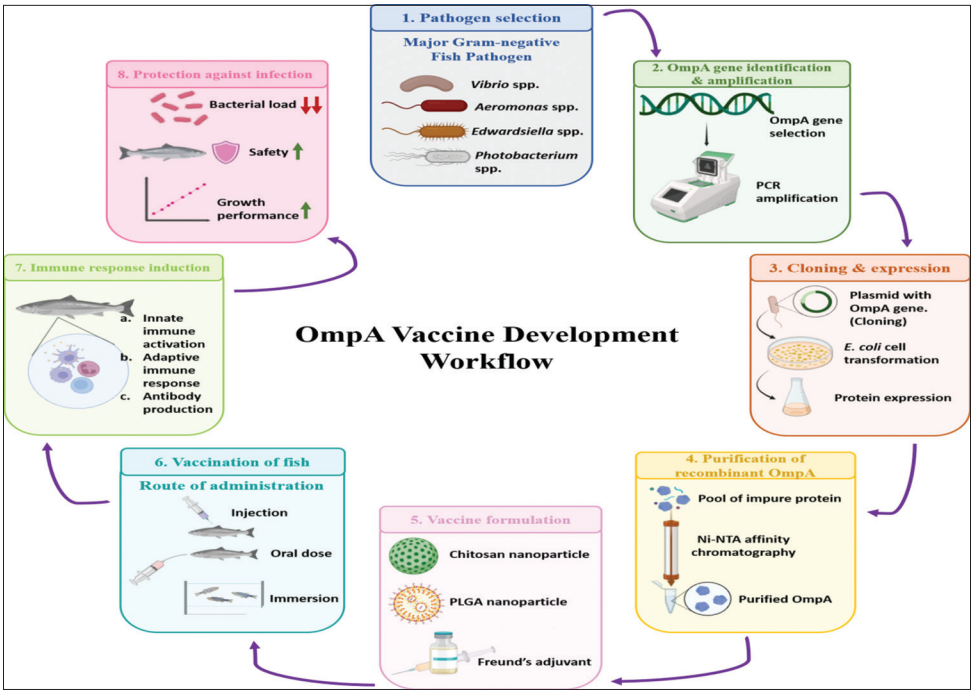


Figure 2: Overall workflow for the development of recombinant outer membrane protein A-based vaccines against bacterial fish pathogens

Immunological mechanisms of OmpA-induced protective immunity

Immunity that is conferred naturally from vaccination using recombinant OmpA is the result of immune responses that are instigated by innate responses to adaptive immunity. After vaccination, the recombinant OmpA is detected by antigen-presenting cells, which activate different pathways that help defend the host against disease and control the infection. Starting with innate immunity, the first response to the vaccine. OmpA activates the immune response mechanisms through its recognition by pattern-recognition receptors that activate phagocytes such as macrophages and polymorphonuclear cells and enhance innate processes such as phagocytosis, respiratory burst, reactive oxygen species production, nitric oxide synthesis, and release of pro-inflammatory cytokines. One way that recombinant OmpA vaccines help provide protection is by coordinating both innate immune responses and specific responses mediated by antibody production, cytokine regulation, and complement and cellular immune activation, as shown in Figure 3. The integrated immune response serves as a biological basis for protective effects in studies of vaccination against bacterial pathogens.

APPLICATION OF OMPA-BASED RECOMBINANT VACCINES AGAINST BACTERIAL FISH PATHOGENS

The rising prevalence of bacterial illnesses in aquaculture has spurred the creation of recombinant subunit vaccines, which are regarded as safer alternatives to conventional bacterins. The antigen that has gained prominence among others is OmpA on account of its location on the surface, its evolutionarily embedded structure, and its diverse biological functions and contribution toward the immune response mechanisms. It is important to point out that the development of recombinant protein production techniques, as well as immunological knowledge, together with advances in immunoinformatics and delivery mechanisms of antigens, proved helpful in investigating OmpA as a basis for vaccines against several major fish bacterial pathogens. The effectiveness of vaccines differs depending on the type of bacteria responsible for the disease as well as vaccine formulation, host fish, and method of immunization, with all the studies revealing a positive impact of OmpA vaccines on fish immune system activity and fish survival after vaccination. The next sections offer a summary of available studies about OmpA-based recombinant vaccines developed to fight major aquaculture bacterial pathogens.[32-34]

CURRENT ADVANCES IN OMPA-BASED RECOMBINANT VACCINES AGAINST BACTERIAL FISH PATHOGENS

The evolution of OmpA-based vaccines has improved a lot due to advances in molecular biology, protein engineering, computational vaccinology, and vaccine delivery technologies. Although early studies only showed the immunogenicity of recombinantly purified OmpA, the focus of current studies is on experimental vaccine

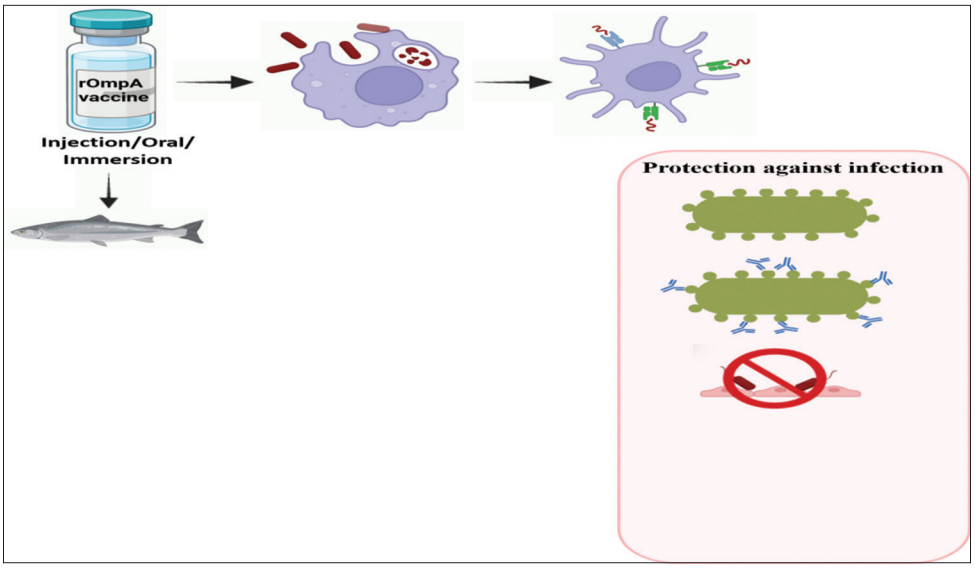


Figure 3: Proposed mechanism of immune protection induced by recombinant outer membrane protein A vaccination in fish

design, immune response improvement, cross-protection capability expansion, and real vaccination application in aquaculture. These developments have made the transition of OmpA-based vaccines from the idea to the stage of next-generation vaccines faster.[35] A major step forward is the utilization of reverse vaccinology, which merges the approaches of whole-genome sequencing and bioinformatics, making it possible to find potential vaccine candidates. As a result, the immune response is broader and more efficient with respect to diverse bacterial strains. Although these vaccines are still under development, they represent substantial progress in vaccine development in fish. The advancements in vaccine administration technologies are noteworthy. Future research will need to address various issues: scalability of production, vaccine stability, regulatory approval, on-field testing, and cost-efficiency. Continuing integration of molecular biology principles with structural vaccinology, nanotechnology, immunoinformatics, and sustainable aquaculture practices can help design commercial OmpA-based vaccines that guarantee high-efficiency protection from bacterial fish pathogens and high durability of protection.

CHALLENGES IN THE DEVELOPMENT OF OMPA-BASED RECOMBINANT VACCINES AGAINST BACTERIAL FISH PATHOGENS

The development of recombinant vaccines based on OmpA has progressed significantly, but several scientific, technical, and practical hurdles continue to hinder their commercial application in aquaculture. Although research studies confirm that recombinant OmpA can trigger protective immune responses against important Gram-negative fish pathogens, its translation into commercial vaccines has been hampered by bacterial diversity, the incomplete understanding of fish immunity, vaccine delivery, production, and field testing. Overcoming these challenges is crucial in designing successful and economically viable vaccination strategies. The main obstacle to the development of effective vaccines includes the genetic diversity of bacterial fish pathogens. In addition, most studies present only short-term control of immunity in laboratory conditions, and little is actually known about the long-term protection in commercial aquaculture. The absence of standardization of research protocols makes it difficult to develop vaccines. The scientific papers published on this topic vary a lot regarding recombinant expression systems, antigen purification technologies, dosage of antigen, adjuvants used, vaccination routes, booster schedules, fish species used, models of infection, and methods for evaluation of the immune response. The differences in the experiments make it complicated to make a comparative analysis and discover the best vaccination techniques.[36] In conclusion, the current obstacles must be considered future opportunities where advancement is possible instead of blocking further progress. It is expected that advances in the field of antigen engineering, immunology in fish, systems of vaccine distribution, and large-scale production will improve the efficacy of vaccines based on OmpA and the economic profitability of these vaccines.

FUTURE PERSPECTIVES OF OMPA-BASED RECOMBINANT VACCINES AGAINST BACTERIAL FISH PATHOGENS

The propagation of aquaculture on the global scale, the rising number of bacterial ailments, and the growing attention to antibiotic resistance have resulted in a much greater demand for safe and sustainable vaccination

methods. OmpA recombinant vaccines show high potential in this area because of their known immunogenic properties, desirable safety profiles, and efficient ability to elicit protective immune responses against a wide range of fish pathogenic Gram-negative bacteria. Injectable vaccines are known for their effectiveness, but oral and immersion immunizations will be more practical for large aquaculture facilities. Biodegradable carriers such as chitosan, poly(lactic-co-glycolic acid), and alginate nanoparticles may be beneficial in terms of preservation of recombinant proteins, providing effective absorption of antigens and controlled antigen release. In general, it is expected that the development in antigen design, computational vaccinology, and biodegradable products will lead to the elimination of the barriers concerning recombinant vaccines for fish.[37,38]

CONCLUSION

The world of sustainable aquaculture is facing great challenges, as bacterial diseases have emerged as the most serious obstacles, emphasizing the need for alternative methods for disease control that do not rely upon antibiotics. Of all recombinant vaccine antigens studied so far, OmpA has appeared as one of the most promising candidates due to its specificity as a conserved protein, its presence on the surfaces of bacteria, and its essentiality in bacterial physiology as well as host-pathogen interactions. Being distinguished by such properties makes OmpA an attractive target for generating protective immune responses and affecting infection-related processes in bacteria. The findings realized in this article demonstrate that recombinant vaccines utilizing OmpA gave positive results in relation to several significant fish pathogens from Gram-negative bacteria, such as *Edwardsiella tarda, Aeromonas hydrophila,* and *Vibrio* species. Findings from experimental studies show that after the application of OmpA-based vaccines, managers of aquaculture have obtained positive results in stimulating both types of immune responses that result in increased resistance to diseases and elevated survival rates in the case of infection. Furthermore, recent achievements in the fields of engineering antigens, structural vaccinology, immunoinformatics, and biodegradable delivery systems have expanded the horizons of improving vaccine efficiency and developing practical vaccination technologies adapted for modern aquaculture. However, successful transfer of these promising research results into commercial vaccine products requires further thorough studies. In future research, the search for protective epitopes belonging to virulence factors, checking of cross-protection against genetically diverse field strains, optimization of methods for oral and immersion delivery of the vaccine, their long-term validation in the field, and organization of cost-effective production must be priorities. Multidisciplinary research that includes molecular biology, fish immunology, vaccine engineering, and biotechnology is likely to boost the development of commercially feasible vaccines based on OmpA. This advancement will significantly reduce dependence on antibiotics, enhance fish health and productivity, and promote sustainability of the fish farming industry globally.

DATA AVAILABILITY

Data will be available on request.

ETHICS APPROVAL

Ethical approval was not required for this research.

CONSENT TO PARTICIPATE

All participants gave their consent to participate.

CONSENT FOR PUBLICATION

The manuscript has never been published in other journals.

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