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ANIMAL SCIENCE

Mechanisms of resistance and tolerance against parasites in fish: the impairments caused by *Neoechinorhynchus buttnerae* in *Colossoma macropomum*

JAQUELINE D. BILLER & EDSANDRA C. CHAGAS

Abstract: Tambaqui is the second native fish most produced species in Brazil. Currently, tambaqui fish farms deals with serious sanitary problems due to the prevalence of the parasite *Neoechinorhynchus buttnerae*. However, the prevalence of the acanthocephalan parasite infections depends on the resistance and tolerance interactions between the host organisms and parasites. The immune response against parasites is divided between innate and acquired immunity. The innate defense is a result of physical barriers, cellular and humoral compounds. Acquired defense occurs through the production of antibodies (humoral) and is mediated by cells, mainly by type 2 T helper lymphocytes. Most parasites secrete a variety of immunomodulatory compounds that allow coexistence with the host and chronicity of the parasite. The host-parasite relationship is complex and makes prevention and treatment difficult. However, some studies show that the use of immunostimulants may have "systemic" effects. These include improvement of the intestinal mucosa health and also in the production of cellular and humoral compounds in the whole body, thus assisting treatment and control. As such, it is important to understand the mechanisms of resistance and tolerance in the host organisms so that prevention and treatment measures can be effective.

Key words: immunity, immunomodulation, tambaqui, Acanthocephala.

INTRODUCTION

Brazilian aquaculture has losses due to disease outbreaks, and it requires more technological research in both public and private sectors in order to reach its full potential. The Brazilian Association of Pisciculture registered fish production of 758,006 metric tons in Brazil in 2019, with a growth of 4.9% in relation to the previous year. The states of Paraná, São Paulo and Rondônia are the main fish producers in Brazil, and Tilapia (*Oreochromis sp.)* is the most produced species at 432,149 tons. The native species, such as tambaqui, pacu and their hybrids, are the second with around 287,930 tons in 2019 (PEIXE BR 2020).

The production of native fish is mainly concentrated in northern, northeastern and midwestern Brazil. The three states responsible for the bulk of production are Rondônia (68,800 tons/year), Pará (25,000 tons/year) and Amazonas state (20,600 tons/year). Tambaqui (*Colossoma macropomum*) is the most produced native species. However, due to climatic, sanitary and market problems, this culture presents economic losses in production (PEIXE BR 2020).

Among the challenges faced by Brazilian aquaculture, fish health is the main issue, because there is high mortality during production. Historically, the diseases occur in aquatic animal farming systems in parallel to aquaculture intensification (Oidtmann et al. 2011). This is because development generally occurs through the introduction of new species and intensification of farming systems, which leads to the emergence of new diseases and the spread of pathogens (Rodgers et al. 2011).

In Brazil, diseases and mortality due to pathogens are often caused by the intensification of production systems. This includes inadequate management and negligence in regards to water quality in the system (De Sant'ana et al. 2012, Lacerda et al. 2012, Videira et al. 2016). As a result, this has lead to severe economic losses in fish production of around 84 million dollars per year due to mortality. However, this loss does not take into consideration the reduction in reproductive potential and the negative impact on feed conversion, both of which decrease growth rates (Tavares-Dias & Martins 2017).

Tambaqui fish farms face several pathogenic diseases, and, the current problem stems from the occurrence of an acanthocephalan, namely *Neoechinorhynchus buttnerae*, which is found mainly in farms in northern Brazil, and causes severe economic losses in production (Malta et al. 2001, Chagas et al. 2015, Dias et al. 2015, Jerônimo et al. 2017, Lourenço et al. 2017, Matos et al. 2017, Pereira & Morey 2018).

It is important to highlight that the occurrence of *N. buttnerae* in tambaqui has not been registered in other regions of Brazil. This is probably due to the lack of fish health monitoring, disease diagnosis and low intensity of production systems. Although this problem has not yet occurred in other regions, measures to avoid parasite spread should still be adopted, given the significant economic losses it causes (Silva-Gomes et al. 2017).

The prevalence of parasitic infections depends on the interactions of resistance and tolerance of the host organisms. The immune response against parasite is divided between innate and acquired immunity. The innate defense is a result of physical barriers, cellular and humoral compounds. Acquired defense occurs through the production of antibodies (humoral) and is mediated by cells, mainly by type 2 T helper lymphocytes. This specific mechanism is classified as classic type 2 response (Dezfuli et al. 2016, Harris & Loke 2017). These responses work together in an attempt to eliminate the parasite and maintain homeostasis. The host-parasite relationship is complex. Most parasites secrete a variety of immunomodulatory compounds that allow coexistence with the host and chronicity of the parasite. This makes prevention and treatment difficult (Dezfuli et al. 2016, Harris & Loke 2017).

However, some studies show that the use of immunostimulants may have systemic effects. These effects include improvements in the health of the intestinal mucosa and also in the production of cellular and humoral compounds in the whole body, which assist treatment and control. Thus, it is important to understand the mechanisms of resistance and tolerance in the host organisms so that prevention and treatment measures can be effective.

FISH IMMUNE SYSTEM

The immune system's purpose is to destroy invaders and, in order to do so, it triggers immune memory processes that are mediated by complex interactions between cells and molecules. The innate system acts more quickly in relation to the specific, and remains active to maintain organic homeostasis. This system includes all the components present in the organism before the appearance of the invader, forming the first organic defense barrier (Bayne & Gerwick 2001, Ellis 2001). Among the components are skin and mucous membranes as the first physical barrier. These contain humoral defense components, such as the complement system, antimicrobial enzyme system, and non-specific mediators such as interferon, interleukins and defense cells. They also contain cell-mediated immunity, such as granulocytes, monocytes, macrophages and natural killer cells (NK) (Ellis 1999). The innate system, by definition, recognizes portions called pathogen associated molecular patterns or PAMPs. These are molecules from infectious agents or normal microbiota such as lipopolysaccharides, peptidioglycans, bacterial DNA or viral RNA, or other molecules found in the membranes of multicellular microorganisms. PAMPs are normally highly-conserved portions during the evolution of species and are present in the vast majority of microorganisms. They are recognized by antigen presenting cells (APCs) through pattern recognition receptors or PRRs (Janeway 1989, Elward & Gasque 2003, Goldsby et al. 2003).

The specific defense system, on the other hand, requires the antigen to trigger reaction cascades that will culminate in the increase of specific circulating antibodies, and trigger immune memory. The receptors of the acquired system are responsible for detecting the invading agent. They are present in the membrane of immunocompetent cells, T lymphocytes (TCR) and B lymphocytes (BCR, surface immunoglobulin), and free in the body fluids and tissues, and known as antibodies. Invading microorganisms are detected by innate antigen presenting cells (APCs, for example macrophages, dendritic cells and B lymphocytes) that process the microorganisms in particles. At first, they trigger immune and proliferation responses and, later, they activate receptors of the acquired system in order to promote expansion of competent cells, production of specific immunoglobulins and memory cells (Bernstein et al. 1998, Abbas & Lichtman 2004).

In regards to defense in fish, the innate immune system is considered more effective than the acquired system, when compared to other higher vertebrates (Magnadottir 2006). This effectiveness is due to the great diversity of genes that encode the PRRs. This ability has occurred through several evolutionary mechanisms (Gomez et al. 2013). However, it is also due to the high variety of prokaryotic (around 1029) and virus (around 1010) cells in the aquatic environment, which trigger the fish's innate system for relevant PAMPS, and restricts acquired immunity in order to adapt to this environment (Gomez et al. 2013, Rauta et al. 2014).

The skin, mucus, epithelium of the gills, and the gastrointestinal tract present physical, chemical and cellular barriers against the pathogen invasion, since they are the main gateways for disease-causing agents. The intestinal mucosa contributes several factors that allow the establishment of normal microbiota. They are produced by lymphoid tissues called gut-associated lymphoid tissue (GALT), which regulate the mucosa immune defense mechanisms (Ellis 1999, 2001, Press & Evensen 1999, Watts et al. 2001, Parra et al. 2015). The defense mechanisms of intestinal mucosa are very important for defense against parasites.

MECHANISMS OF RESISTANCE AND TOLERANCE TO HELMINTHS: MOLECULAR BASES OF TYPE 2 IMMUNITY

Most wild vertebrates harbor parasites, among them, the most common are intestinal nematodes that can remain in the intestine for prolonged periods, often causing only morbidity, though not mortality. The problem is that there is great difficulty in preventing and treating parasitic disease due to the characteristics of this parasite-host relationship. The prevalence of parasitic infections depends on the resistance and tolerance interactions of the host organisms (Harris & Loke 2017). Resistance mechanisms promote the parasite's expulsion and the prevention of reinfection, whereas tolerance mechanisms reduce responses against parasites, and allow high parasitic load. (Harris & Loke 2017). Highly infected individuals have low resistance and high tolerance to parasites, and are unable to expel the parasites because of weak immune responses against these organisms. Highly-resistant and poorly-tolerant individuals, on the other hand, may present immune responses capable of expelling the parasites, and usually present clinical signs resulting from the immune-mediated pathology that is triggered by the parasite. This is a strategy to ensure that the presence of the parasite does not harm the survival of the host (Hotez et al. 2008).

Intestinal lesions caused by parasites are generally neither visible nor severe, mainly due to their superficial relationship with the host, however some species, such as Acanthocephala, generally cause much more serious damage due to deep penetration of intestinal tissue (Reite 2005, Taraschewski 2000). The parasite triggers local inflammatory response, with the influx of neutrophils and monocytes/macrophages, and an increase in mucous cells and/or mucus production and mast cell degranulation. Acquired defense happens through the production of antibodies (humoral) and is mediated by cells, mainly by type 2 T helper lymphocytes. This specific mechanism is classified as classic type 2 response. (Dezfuli et al. 2016). These responses work together in an attempt to maintain homeostasis and are characterized by a cellular and cytokine repertoire, which act according to the host's resistance against parasite infections (Dezfuli et al. 2016, Lloyd & Snelgrove 2018).

The response against parasites is strongly associated with immunity mediated by type 2 T helper lymphocytes, and it is present in several species, such as fish, mice and humans (Maizels & Yazdanbakhsh 2003, Dezfuli et al. 2016). Type 2 immunity has cellular and tissue processes that are characterized by the release of the cytokines IL-4, IL-5, IL-9 and IL-13, which are normally associated with adaptive T helper lymphocyte 2 (Th2). However, recently, the study of these pathways in innate immunity has been widely publicized due to the discovery of group 2 innate lymphoid cells (ILC2), which are the main innate sources of IL-5 and IL-13. These cytokines promote the recruitment of eosinophils and the activation of macrophages (Kotas & Locksley 2018, Walker et al. 2015). Immune responses mediated by type 2 cells influence resistance (Grencis 2015) and tolerance in helminth infections (Medzhitov et al. 2012).

ILC2 have the capacity to secrete large amounts of type 2 cytokines in the absence of adaptive immunity and are involved in several biological processes such as wound healing, control of metabolic homeostasis and temperature (Lloyd & Snelgrove 2018). LIC2 are a subset of lymphocytes that have been recently described, and are present in peripheral tissues, the spleen, liver, Peyer's patches, lymphoid nodules. They are particularly abundant on barrier surfaces such as the gastrointestinal tract. ILC2 are an evolutionary strategy for early attack against invaders, and usually respond around 1-4 hours after contact with stimulus (Kotas & Locksley 2018, Moro et al. 2010, Neill et al. 2010, Price et al. 2010).

Innate lymphoid cells (ILC2) are derived from common helper lymphoid progenitor cells (T helper), which differentiate into ILC2 after activation of GATA3, Bcl11b, RORα, TCF-1, and Gfi1 transcription factors. ILC2s do not have antigen receptors, such as T and B cells, but are directly stimulated by the cytokines IL-33 and IL-25, which are derived from injured epithelial cells (Kabata et al. 2018). The activation of ILC2 by IL-33 and IL-25 cytokines promotes the release of cytokines and peptides, such as IL-4, IL-5, IL-6, IL-9, IL-13, GM-CSF, amphiregulin, eotaxin and methionine-enkephalin (Met-Enk), which results in macrophage and eosinophil recruitment that expresses the genes involved in tissue repair, but also decreases in the type 1 immunity (common in bacterial and viral infections) (Knipper et al. 2015). ILC2s also prompt production of mucus and epithelial repair proteins of barrier tissues (to repair damage caused by parasites), and activate basophils, intestinal mast cells and B cells. In addition, they prompt production of immunoglobulins that are parasite-specific (Kabata et al. 2018, Finkelman et al. 2004, Harris & Loke 2017). The interleukins IL-4 and IL-13 are canonical cytokines of type 2 immune response. They are primarily responsible for eliminating adult parasites, and are therefore targets of studies of several species (Bao & Reinhardt 2015, Harris & Loke 2017, Sequeida et al. 2020, Zhu 2013, Wang & Secombes 2015).

The host-parasite relationship is complex. Most parasites secrete a variety of immunomodulatory compounds that allow coexistence with the host and chronicity of the parasite. (Maizels & Yazdanbakhsh 2003). The intestinal microbiota and parasites have evolved together to co-inhabit the same tissue, and the host's ILC2-mediated response plays a critical role in altering the microbiota after parasitic infestation, thus favoring certain bacterial communities (Harris & Loke 2017). Studies on gut infection have contributed to the expansion of knowledge of cellular and molecular responses, as well as the understanding of type 2 cell-mediated immunity. Innate lymphoid cells (ILC2) are known to exist in higher animals, but our hypothesis is that in fish their function is much more important, just as innate immunity is more important that acquired immunity, when compared to other animals. There is evidence that the ILC2 have an influence on the resistance against parasites in higher animals, but poorly known in fish (Harris & Loke 2017, Kabata et al. 2018).

GUT IMMUNITY: ROLE OF TGI IN DEFENSE AGAINST PARASITES

Mucous surfaces, such as the gastrointestinal tract, are the fish's first innate barrier of defense against external aggressions, including those from organisms present in aquatic environments (Cordero et al. 2016, Guardiola et al. 2017). Mucus is a viscous layer composed of colloidal gel secreted by several cell types, such as goblet cells, which cover all epithelial tissue. Its location represents the interface between the external and the internal environment, giving it great importance as the first defense barrier (Guardiola et al. 2017, Patel & Brinchmann 2017). Mucus consists of 90% to 95% water and 1% to 5% mucins, which are glycoproteins conjugated to high molecular weight oligosaccharides that have high adhesiveness (mucin carbohydrates bind with microorganism receptors) and renewal power, leading to prevention of microorganism adhesion in the epithelial cells (Cone 2005). Mucus contains cytokines, glycoproteins, lysozyme, immunoglobulins, complement system proteins, lectins, C-reactive protein, flavoenzymes, proteolytic enzymes and antimicrobial peptides with inhibitory or lytic actions. These are produced by competent cells in lymphoid tissues associated with the gut-associated lymphoid tissue (GALT), which are found in the skin, gills and gastrointestinal tract (Guardiola et al. 2017, Shephard 1994, Patel & Brinchmann 2017).

Currently, proteomic mapping of gut mucosa is being performed in the search for molecules that are involved in protecting the epithelium against disease-causing agents (Cordero et al. 2016, Patel & Brinchmann 2017), as well as the expression of genes from GALT cells that are responsible for the production of defense compounds (Ren et al. 2015, Douxfils et al. 2017). Molecules, such as lysozyme, IgM, proteases, antiproteases, peroxidases and alkaline phosphatase, have been characterized and have an efficient action in protecting against invading agents (Nigam et al. 2012, Guardiola et al. 2014). However, endogenous factors, such as the stage of development, and external factors, such as stress, an acidic environment and infections, can impair the efficiency of such protective molecules (Sanahuja & Ibarz 2015). On the other hand, several studies have observed beneficial changes in mucus composition modulated by different compounds, such as immunostimulants (Cordero et al. 2015, 2016, Dawood et al. 2016).

Gut mucosa immunity plays a significant role in the fish's defense mechanism, since the parasite must overcome this first barrier to enable co-existence. Thus, the knowledge of the specific elements produced by gut epithelium can bring us greater understanding of host-parasite relationships and collaborate with necessary measures to combat this problem in aquaculture.

Colossoma macropomum

Tambaqui (*Colossoma macropomum*) is a freshwater fish species, native to the Amazon Basin and the Orinoco River. It belongs to the Characiformes order and the Serrasalmidae family, and its production has grown significantly in Brazilian fish farming in recent years. As such, it is now the main cultivated native species in Brazil (IBGE 2018). Tambaqui and its hybrid versions tambacu (*C. macropomum x Piaractus mesopotamicus*) and tambatinga (*C. macropomum x P. brachypomus*) are widely farmed in fish farms in South America (Valladão et al. 2018). However, there has been an increase in diseases on the farms in parallel to the increase in production that has caused losses, which are mainly due to the decrease in feed conversion and, consequently, fish weight loss in these species (Malta et al. 2001, Tavares-Dias et al. 2011, Santos et al. 2013, Videira et al. 2016).

In recent years, records of infection by *N. buttnerae* have been recurrent and tambaqui have presented high rates of infections in fish farms (Chagas et al. 2015, Jerônimo et al. 2017, Aguiar et al. 2018). Silva-Gomes et al. (2017) demonstrated significant economic losses in the production of tambaqui due to infection by *N. buttnerae* that included a reduction of over 200% in productivity indexes, such as weight loss, final biomass and production by area, and which resulted in a decrease in the producers' gross revenue. Despite efforts in research to develop effective treatments, few products traditionally adopted by veterinary medicine have had satisfactory efficacy in eliminating the acanthocephalans (Valladão et al. 2019).

The aquaculture industry seeks technological advances to obtain products to treat and control parasites. Currently the most used methods are the conventional synthetic anthelminthic and chemotherapy administration in water, in the feed or injected in fish. However, there are several researches for ecological, non-toxic and natural therapies, with less toxicity for fish and workers, being a strategy to increase the general sustainability of the activity (Costa et al. 2020, Gonzales et al. 2020).

A recent study has shown an increase in the immunoglobulin titers in the plasma of tambaqui infected with *N. buttnerae*, but a decrease in the intestinal mucus and alkaline phosphatase levels (Melo-Souza 2019). Da Cunha et al. (2020) found a decrease of 45% in the RAG2 gene and 80% MALT1 gene expressions of *N. buttnerae* infected tambaqui when compared with non-infected control. Our hypothesis is that tambaqui exhibit high tolerance and low resistence to *N. buttnerae,* since there was immune suppression after parasite infection.

Neoechinorhynchus buttnerae

The phylum of worms known as Acanthocephala are the smallest group of parasites with approximately 1,100 species (Bush et al. 2001). More than a half of the species are fish endoparasites and occur in wild or farm animals (Nickol 2006). The life cycle of this group is indirect and is based on the food chain. They require an arthropod as an intermediate host and a vertebrate as the definitive host, however, paratenic hosts may be present (Santos et al. 2013). In general, crustaceans are listed as intermediate hosts for acanthocephalans (Santos et al. 2013). The ostracoda *Cypridopsis vidua* is an intermediate host in the life cycle of *N. buttnerae* and harbors it for 29 days until the parasite's development into the cystacanth stage, which is considered the infective form for tambaqui (Lourenço et al. 2018).

N. buttnerae belongs to the Neoechinorhynchidae family, and is a specific parasite of *C. macropomum*, but it has also been registered in the hybrid versions of the fish (Dias et al. 2015, Jerônimo et al. 2015). This species has a small proboscis in relation to the rest of the body. It is spherical with approximately 0.30 mm in diameter, and has the characteristic hooks. The receptacle is inserted at the union of the neck with the proboscis, and the nervous ganglion is located at the bottom of this structure (Golvan 1956).

The proboscis, in the anterior region of the body, is used for fixation in the host's intestine. Depending on the size of the proboscis, the size of the spines and the number of individuals, these parasites can cause either superficial, deep damage or more serious injuries (such as bleeding). In addition, acanthocephalan infections can cause mild to more severe damage, mainly related to the degree of penetration of the proboscis in the intestine (Dezfuli et al. 2016). Tambaqui infected with *N. buttnerae*, mainly in high intensities, have macroscopical thickening and hardening of the intestinal wall. Histologically, an intense inflammatory reaction is observed, which is characterized by the presence of macrophages, dendritic cells and some lymphocytes, with the formation of granulomas in the submucosal layer of some animals (Jerônimo et al. 2017). More severe tissue damage has been observed in places where the proboscis has penetrated, such as leukocyte cell infiltration, muscle tissue metaplasia, and necrosis affecting all layers of the intestine (Matos et al. 2017).

IMMUNOSTIMULANTS

The beneficial action of immunostimulants in the treatment against parasites has already been observed in other species. The use of immunostimulants has gained attention due to the diverse biological functions that these compounds have in many fish species (Albuquerque et al. 2020). Several studies demonstrate beneficial action of immunostimulants, probiotics, plant extract and other compounds administration (not classified as antibiotics) in controlling or treating parasites in fish (Reverter et al. 2014, Rodriguez-Tovar et al. 2011). Benvoka et al. (1992) suggest the administration of β-glucan for fish prophylactic treatment.

β-glucan is one of the most studied and applied immunostimulants in fish, however its mode of action is not completely understood, and there is a gap in the knowledge of the whole body systemic action of this compound, including its action on GALT and on the defense molecules found in mucus (from the skin, gills and intestine). β-glucan administered through the diet is recognized by receptors in the GALT of gut mucosa, and leads to the stimulation of antioxidant and immunological activity through the modulation of phagocyte responses, cell proliferation, activity of natural killer cells and levels of humoral defense compounds, such as lysozyme and complement system proteins, acting in the whole body (Dawood et al. 2015a, 2017).

The recognition of β-glucan by the PRRs of cells triggers reactions that stimulate the innate defense system through the expression of pro and anti-inflammatory genes (Vallejos-Vidal et al. 2016). However, this immunostimulant can also induce changes in the composition of the intestinal microbiota and, thus, indirectly influence the defense system, resulting in an increase in resistance to diseases (Dalmo & Bogwald 2008).

Dawood et al. (2017) observed an increase in lysozyme, bactericidal activity and peroxidase, in addition to an increase in the amount of mucus in the epidermis produced by *Pagrus major* fed with β-glucan. As such, immunostimulants, in addition to the benefits already known on productive performance, can promote a systemic action on the GALT and consequently on the mucus molecules (Dawood et al. 2015a, b, 2017). Schmitt et al. (2015) characterized the immune mechanisms of intestinal mucosal epithelial cells after administration of β-glucan in trout, and observed an increase in the expression of defense peptides, catelicidins and IL-1β.

β-glucan administered in animal diets is considered a PAMP, and they are recognized by specific receptors in phagocytes, internalized by phagocytosis, and processed by reactive oxygen and nitrogen species, in addition to lysosomal lytic enzymes, in the phagolysosome. The phagocytosis process, which is fundamental for the destruction of pathogens, but also for the induction of acquired defense, is stimulated by this immunostimulants, which leads to an increase in the production of reactive oxygen species (ROS) that are fundamental for the destruction of the invading agents (Goodridge et al. 2011).

β-glucan has a potent action for increasing the concentration of lytic proteins, such as lysozyme and those of the complement system, in addition to stimulating the phagocytic activity of macrophages (Robertsen et al. 1990, Chen & Ainsworth 1992, Engstad et al. 1992, Galeotti 1998, Ortuno et al. 2001). These protect against many diseases (Jeney & Anderson 1993, Santarém et al. 1997, Verlhac et al. 1996). Further studies should be carried out to evaluate immunostimulants administration on *C. macropomum* defense against parasite.

FUTURE PERSPECTIVES

Elucidating the mechanisms of resistance and tolerance against *Neoechinorhynchus buttnerae* in *Colossoma macropomum* can help in the treatment and prevention of the disease. Gut mucosa immunity plays a significant role in fish defense, since the parasite must overcome this first barrier to enable co-existence. Thus, the knowledge of the specific elements produced by the gut epithelium can improve understanding of host-parasite relationships and collaborate with necessary measures in order to combat this problem in tambaqui aquaculture.

New studies on gut infection contribute to the expansion of knowledge regarding cellular and molecular responses, as well as the understanding of type 2 cell-mediated immunity. Innate lymphoid cells (ILC2) are known to occur in higher animals, but our hypothesis is that in fish its function is much more important, just as innate immunity is more important than acquired immunity, when compared to other animals. This information is important for understanding the fish's immune system against the *N. buttnerae* and to contribute to parasitic disease control.

The study of how these parasites promote chronic infections without evident clinical signs are essential for the development of new eradication strategies, as well as to prevent outbreaks and losses in aquaculture production, and will contribute to the search for new treatments, new drugs or vaccines.

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JAQUELINE D. BILLER[1]
https://orcid.org/0000-0001-6034-2350

EDSANDRA C. CHAGAS[2]
https://orcid.org/0000-0001-9170-9725

[1]Universidade Estadual Paulista/UNESP, Faculdade de Ciências Agrárias e Tecnológicas, Departamento de Produção Animal, Campus de Dracena, Rodovia Comandante João Ribeiro de Barros, Km 651, Bairro das Antas, 17900-000 Dracena, SP, Brazil

[2]Empresa Brasileira de Pesquisa Agropecuária - Embrapa Amazônia Ocidental, Rodovia AM 010, Km 2, Caixa Postal 319, Zona Rural, 69010970 Manaus, AM, Brazil

Correspondence to: **Jaqueline Dalbello Biller**
E-mail: jaqueline.biller@unesp.br

Author contributions

Each author presented a relevant contribution to elaboration of the present manuscript as follows: Jaqueline Dalbello Biller reviewed fish immunity, including parasite immunity, mucosal immunity and use of immunomodulators in fish. In addition was the main responsible for the final text. Edsandra Campos Chagas reviewed the state of the art of native fish production in Brazil, including the review on tambaqui and parasites. In addition, I was responsible for the final text.