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Epidermal mucus as a potential biological matrix for fish health analysis

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ABSTRACT

Epidermal mucus serves as a physiological and immunological first line of defense to maintain normal physiological status in Teleost fish. It offers protection against pathogenic infections and environmental contaminants. The ability of mucus as a protector depends on its bioactive components, such as high-molecular-weight glycoproteins, lysozyme, alkaline phosphatase, immunoglobulin, complement proteins, C-reactive proteins, lectins, agglutinin, interferon, vitellogenin, proteases, antimicrobial proteins, antimicrobials peptides, calmodulin, crinotoxins, pheromone, cytokines, acute-phase proteins, carbonic anhydrase, hemolysin, serotransferrin, heat shock proteins, superoxide dismutase, and pentraxins. Cortisol, glucose, lactic acids, reactive oxygen species, and cellular antioxidants were also detected in the epidermal mucus and have the potential as stress biomarkers. Aside from its potential as a biological matrix to assess the immunity and health status of fish, epidermal mucus also serves as an ecotoxicological biomonitoring tool by detecting biochemical biomarkers responses that arise. We encourage future studies to assess the potentials of the epidermal mucus biological activity using the proteomics approach, given the diversity of fish species. Knowledge about fish health and welfare is important for the conservation and preservation of species biodiversity.

INTRODUCTION

Stress and disease in fish often occur in the aquaculture industry and the aquatic environment. Microbial infection, water quality, and improper management are factors that may cause stress and disease in fish (Guardiola *et al*., 2016). Fish live in an environment surrounded by microbes. Its skin is susceptible to infection because of contact and exposure to water microorganisms. The decrease in water quality occurs because of changes in dissolved oxygen, water pH, carbon dioxide, temperature, salinity, photoperiod (Cabillon and Lazado, 2019), ammonia pollution (Al-Zaidan *et al*., 2013) and heavy metals pollution (Omidi *et al*., 2020). Stress caused by management factors includes crowding, nutritional deficiencies, and improper handling in sorting, storage, or transportation, resulting in adverse effects on fish physiology (Albaladejo-riad *et al*., 2020). Stress can reduce the body's immune system, reducing resistance to pathogenic invasion and affecting the survival of fish, which makes it susceptible to disease. Fish has a complex defence system mechanism to ward off stress and disease, one of which is the mucous layer as a mucosal defence system that serves as (i) a stable physical and biochemical barrier against pathogenic invasion and environmental pressures such as exposure to pollutants, (ii) coatings that protect epithelial cells in gills, skin, and gastrointestinal tissues. The bioactivities of the mucous layer are a key mechanism in the innate immune system in fish. Weak mucus activities in the first line of defence resulted in disease.

Pressure on the aquatic environment because of anthropogenic factors such as pollution also results in oxidative stress, therefore fish must have a strong host defence system. Fish skin is susceptible to pollutants and is the target of oxidative stress, so it requires routine ecotoxicological biomonitoring. Monitoring of water pollution in the last decade have used epidermal mucus as a potential biological matrix to analyze oxidative stress biomarkers with non-invasive methods for early detection of stress responses and for tracing the effects of pollutants in fish (Omidi *et al*., 2020; Montenegro *et al*., 2020). Using skin mucus as a biological matrix in monitoring fish health status is in line with the principle of environmental conservation because, in its analysis, it does not lead to stress, wounds, or death in fish, especially in endemic and protected rare fish. The epidermal mucus has also been used as early detection in monitoring fish health status in the aquaculture industry against pathogenic invasion, especially bacteria, viruses, and parasites. Mucus with mucins as its key components is a slimy, slippery layer, covering the epidermal surface, in the form of viscous colloids containing antimicrobial bioactive compounds, proteins, lipids and water. Epidermal mucus serves as an important component of the innate immune system mechanism in two ways, first by producing mucus continuously to form antibiofilm agents and releasing them regularly. This prevents the pathogens from invading again or as an anti-adhesion to the formation of stable colonization by potentially infectious microbes and blocking parasitic invasion (Dash *et al*., 2018; Patel *et al*., 2020). Secondly, epidermal mucus has also been shown to have antimicrobial activity mediated through a series of innate immune factors such as lysozyme, immunoglobulin, complement proteins, lectins, C-reactive proteins, proteolytic enzymes, proteases, alkaline phosphatase, antibacterial proteins, and antimicrobial peptides (Dash *et al*., 2018; Omidi *et al*., 2020; Ghalambor *et al*., 2020). Antimicrobial peptides secreted by immune cells and released into mucus are piscidin, epinecidin-1, and chrysophsins (Fekih-Zaghbib *et al*., 2013). Other bioactive components of epidermal mucus are cytokines, acute-phase proteins, carbonic anhydrase, and hemolysin (Dang *et al*., 2020). Therefore, fish relies heavily on its innate immune system because its adaptive immune system is relatively underdeveloped (Ángeles Esteban, 2012). Besides, cortisol, glucose, and lactic acid detected in epidermal mucus have the potential to be stress biomarkers. (Guardiola *et al*., 2016; Fernández-Montero *et al*., 2020; Ouyang *et al*., 2020). Other biomarker responses are the excessive production of reactive oxygen compounds and the detection of cellular antioxidants in epidermal mucus, which also acts as an early detection method of oxidative stress in fish (Dzul-Caamal *et al*., 2016a; 2016b).

This paper reviews (i) fish's skin mucus components and their bioactivities in response to stress due to pathogenic invasion and environmental pressure; (ii) biochemical responses detected in fish skin mucus as stress biomarkers. Biomarkers in mucus have the potential as a non-invasive method for early detection in evaluating fish stress and health status. We expect the use of mucus biochemical responses as biomarkers to be increasingly popular to assess sub-lethal effects in fish. Thorough understanding of the biological activity of fish skin mucus components and biochemical responses to stress-related mucus will provide thorough knowledge on the mechanisms of the fish's mucosal immune system that are useful for (i) assessing fish health status to develop health management in the modern aquaculture industry and ecotoxicological biomonitoring studies; (ii) facilitate the development of new vaccination strategies and the development of therapeutic applications in fish.

REVIEW

Epidermal mucus components

Teleost fish mucus is similar to mammal mucus, which mainly composed of mucins (Shephard, 1993). Mucins are produced by goblet cells, club cells, and sacciform cells in the fish epithelium (Reverter *et al*., 2018; Xiong *et al*., 2020). Sticky gel-shaped mucin, insoluble in water, comprising glycoproteins containing high-molecular-weight oligosaccharides (Gobi *et al*., 2018). Mucins determine the viscoelasticity and rheology of epidermal mucus (Ángeles Esteban, 2012). Mucins serve as a mechanical barrier that filters and prevents pathogenic invasion against the underlying tissue. Epidermal mucus is known as an important element in the mucosal barrier and immune system of fish (Dang *et al*., 2020). The bioactivity of the epidermal mucus as an antimicrobial depends on the function of its constituent components, namely proteins, carbohydrates, lipids, water, and metabolites (Dash *et al*., 2018). Fish skin mucus contains different fatty acids, namely saturated fatty acids, monosaturated fatty acids, and polyunsaturated fatty acids. The saturated fatty acids in epidermal mucus are palmitic acids and stearic acids. Monosaturated fatty acid is oleic acid. The polyunsaturated fatty acids are linoleic, alpha-linolenic, and moroctic acid. These fatty acids serve as a defence against pathogenic invasion (Dash *et al*., 2018). Fish skin mucus is also reported to contain several metabolites that have antibacterial properties such as azelaic acid, N-acetylneuraminic acid and N-acetylglucosamine, and hydroxyisocaproic acid (Ekman *et al*., 2015).

Some researchers have identified the bioactive components of epidermal mucus, i.e. high-molecular-weight glycoproteins (~ 106 kDa) (Subramanian *et al*., 2008), lysozyme (Abolfathi *et al*., 2020), alkaline phosphatase (Guardiola *et al*., 2014; Dash *et al*., 2018), immunoglobulin (Salinas, 2015), complement proteins (Salinas, 2015; Magnadóttir *et al*., 2019), lectins (Cordero *et al*., 2016), agglutinin, interferon, vitellogenin (Gobi *et al*., 2018), proteolytic enzymes, various types of proteases including trypsins, metalloproteases and cathepsin (Dash *et al*., 2018) and some antimicrobial proteins and antimicrobial peptides that protect fish against pathogenic invasion (Abolfathi *et al*., 2020). Epidermal mucus also contains calmodulin (Patel and Brinchmann, 2017), crinotoxins (Reverter *et al*., 2018), pheromone (Bulloch *et al*., 2020), cytokines, acute-phase proteins, carbonic anhydrase, hemolysin (Dang *et al*., 2020), serotransferrin, heat shock proteins, superoxide dismutase (Xiong *et al*., 2020), and pentraxins (Magnadóttir *et al*., 2019).

Epidermal mucus bioactivities as a stress response

Mucus covers the skin and gills of fish as the first surface layer. It always in contact with the aquatic environment so that the emerging biochemical responses are suitable as biomarkers for early detection of stress or disease because of pathogenic invasion and environmental pressures (Dzul-Caamal *et al*., 2016). Fish skin mucus according to Tarnawska *et al*. (2019) has been used as stress biomarkers, among others, by detecting antioxidant activities, enzymes (esterases, proteases), non-enzymatic proteins (vitellogenin, radiata zone proteins), hormones (cortisol), and innate immunity. According to Reverter *et al*. (2018), molecular bioactivities in fish skin mucus serve as an antimicrobial, innate immune system, cellular metabolism, carbohydrate metabolism, lipid metabolism, and protection against ultraviolet exposure. Molecular bioactivities in fish mucus also involved in ecological interactions such as same-sex communication, as cues of finding suitable habitat, partners, or as an alarm signal to danger.

Epidermal mucus serves as a dynamic physical and biochemical protection, and biological and ecological activities such as; communication, sensory perception, locomotion, respiration, ion setting, osmoregulation, excretion, and temperature setting (Ángeles Esteban, 2012), protection against friction, protection against environmental toxins and heavy metal toxicity, parental feeding, and protection against pathogens (Dzul-Caamal *et al*., 2016; Reverter *et al*., 2018). Epidermal mucus is dynamic and semipermeable which allows the exchange of nutrients, water, gas, aroma, hormones, and gametes. Epidermal mucus also acts as a biological barrier because its component activities involved in the immune response can trap or immobilize pathogens so they cannot penetrate the epithelial layer of the epidermis (Cone, 2009; Ángeles Esteban, 2012; Gobi *et al*., 2018). Stressed fish due to exposure to chemical pollutants such as heavy metals, secreted more mucus as a barrier, inhibiting the diffusion of chemicals. Mucus can bind organic and inorganic materials and eliminate those materials by expelling them into the environment. Consequently, chronic toxin exposures to the mucosal epithelium layer decrease the number of mucosal cells and the thickness of the epithelium layer (Dang *et al*., 2019). The mucosal barrier in the skin, gills, and intestines of fish is essential as an ecotoxicological biomonitoring tool.

The composition and characteristics of epidermal mucus such as rheological and viscoelasticity properties are essential to supporting their functional activities in the innate immune system (Lai *et al*., 2009). The content of bioactive compounds and fish mucus characteristics varies depending on fish species, endogenous factors such as gender and developmental stage, and exogenous factors such as stress, hyperosmolarity, temperature, pH, and infection (Ángeles Esteban, 2012). Stress conditions (e.g., crowding, stress handling, nutrient deprivation, ammonia pollution, and exposure to toxic substances) may affect the production and composition of mucus bioactive compounds, disrupt the fish health status and increase its susceptibility to pathogenic bacteria (Al-Zaidan *et al*., 2013; Terova *et al*., 2011; Easy and Ross, 2010; Liu *et al*., 2013; Reverter *et al*., 2018). Stressed and injured fish contain a lot of protein in their skin mucus

(Ángeles Esteban, 2012). Mucus viscoelasticity determines its ability to withstand bacterial motility. Several studies suggest that when stressed, fish will produce mucus continuously (Cone, 2009), increase its mucus secretion and change its mucus composition (van der Marel et al., 2010; Gustafsson *et al*., 2013; Rajan *et al*., 2013).

Bioactivities of fish epidermal mucus as a stress response in this review focuses on (i) the bioactive components of the epidermal mucus that play roles in the mucosal immune system, (ii) the bioactive components of the epidermal mucus that function as antimicrobials and (iii) the epidermal mucus as a potential biological matrix to analyze oxidative stress biomarkers due to environmental pressures such as heavy metal pollution and aromatic polycyclic hydrocarbons.

Epidermal mucus bioactivities in innate immunity

Teleost fish has an active mucosal immune system (Ángeles Esteban, 2012; Salinas, 2015). The mucosal immune system is composed of innate and adaptive immune cells and molecules that work together to protect the host from pathogenic invasion (Guardiola *et al*., 2016). Thus, fish has a vital component in the defence system which is mucosa-associated lymphoid tissue (MALT). MALT found in the skin is called skin-associated lymphoid tissue (SALT) in the gills called gill-associated lymphoid tissue (GIALT), in the nasopharynx is called nasal-associated lymphoid tissue (NALT) and in the digestive tract is called gut-associated lymphoid tissue (GALT) (Salinas, 2015; Guardiola *et al*., 2016; Cabillon and Lazado, 2019). Thus, fish skin contains SALT and various types of leukocytes such as lymphocytes, granulocytes, and macrophages, which quickly migrate to the site of infection to kill pathogens (Xiong *et al*., 2020). Other cellular components that contribute to the fish's innate immunity are mast cells and mucosal dendritic cells (Reverter *et al*., 2018).

Lately, epidermal mucus is used as a source for proteomic mapping and the discovery of new protein molecules involved in mucosal immunity (Cordero *et al*., 2016; Fæste *et al*., 2020; Xiong *et al*. 2020). A metabolomic approach to fish skin mucus has been used to monitor the health status of fathead minnow (*Pimephales promelas*) by detecting 204 different metabolites (Ekman *et al*., 2015). Meanwhile, Fæste *et al*. (2020) with the proteomics approach has succeeded in identifying 1192 proteins from Atlantic salmon skin mucus. A total of 918 proteins has been identified by Xiong *et al*. (2020) of 54443 spectra which refers to the yellow catfish (*Pelteobagrus fulvidraco*) genome database. The proteomics approach has identified that proteins such as lectins, complement proteins, antimicrobial peptides, and immunoglobulins play roles in innate immunity. Proteomics data provide information about protein profiles to comprehensively understand the function and biological activity of fish skin mucus in fighting microbial infections. These proteins are detected in mucus, so it is useful for evaluating the stress and health status of fish (Fæste *et al*., 2020; Xiong *et al*., 2020; Dang *et al*. 2020). Epidermal mucus is also a source for analyzing changes in a humoral immune activity such as immunoglobulin, lysozyme, or alkaline phosphatase (Cordero *et al*., 2016). Mucosal immunity in the epidermal mucus of fish depends on ecological and physiological conditions such as seasonal cycles and developmental stages. For example, lysozyme levels are affected by the seasonal cycles. In the season when the risk of contracting diseases are high, lysozyme levels in mucus and blood will increase. The stages of immune system development show that the younger the level of immune maturity, the lower the ability to kill pathogens. The integrity of epidermal mucus is very essential for the welfare and survival of fish (Abolfathi *et al*., 2020).

The bioactivities of epidermal mucus in innate immunity depend on its protein components such as lysozyme, phosphatase, esterases, proteolytic enzymes, complement proteins, lectins, immunoglobulins, and C-reactive proteins. The activities of these protein components seek to eliminate pathogens and produce immunity when infection occurs (Reverter *et al*. 2018; Ghalambor *et al*., 2020). Lysozymes, alkaline phosphatases, and proteases have acted as hydrolytic enzymes in rainbow trout skin mucus (Abolfathi *et al*., 2020). Lysozyme is an enzyme that breaks the bond of β-1,4-glycosidic between N-acetyl glucosamine-acid and muramic N-acetyl acid in peptidoglycan, so it can damage the cell walls of bacteria in hypoosmotic environmental conditions (Dash *et al*., 2018; Abolfathi *et al*., 2020; Srichaiyo *et al*., 2020). Lysozyme found in epidermal mucus plays a role in the mucosal defence mechanism against bacterial, viral and parasitic infections (Guardiola *et al*., 2014; Ghalambor *et al*., 2020; Abbas *et al*., 2020). Estimation of lysozyme levels is diagnostic to determine fish disease status (Abbas *et al*., 2020). Acid and alkaline phosphatases and esterases are important enzymes in fish epidermal mucus, which have antibacterial agents and potential indicators of stress (Ross *et al*., 2000; Nigam *et al*., 2014). The activity of the alkaline phosphatase enzymes in the epidermal mucus of fish is an antibacterial agent and helps to heal wounds (Easy and Ross, 2010). Protease is a catalytic enzyme to hydrolyze protein peptide bonds. Fish epidermal mucus contains various proteases that play a role in the innate immune system mechanism. Proteases eliminate the function of pathogens, and other foreign substances (Dash *et al*., 2018; Abolfathi *et al*., 2020). Various types of protease enzymes detected in epidermal mucus are trypsins, serin, metalloproteases, cathepsin, and aminopeptidases (Abolfathi *et al*., 2020), with serin and metalloproteases being the most dominant (Ángeles Esteban, 2012). Proteases are expressed in response to various immune stimulants, including injuries and pathogenic bacteria invasion (Albaladejo-riad *et al*., 2020). Lectins are a protein that binds to carbohydrates expressed on the cell surface and can clump pathogenic cells that live in the epidermal mucus. They can coagulate bacteria on the surface of mucous cells by recognizing specific sites on glycoproteins and glycolipids or polysaccharides in bacteria. In the epidermal mucus, lectins play active roles in the mucosal defence system with its activity on the external surface of the body (Dash *et al*., 2018). Some complementary proteins such as C7, C3, and C9 have been identified in the epidermal and intestinal mucus of several fish species (Shen *et al*., 2012; Fan *et al*., 2015; Salinas, 2015; Reverter *et al*., 2018). Immunoglobulins (IgM and IgT/IgZ) are the key components of innate immunity in the epidermal mucus, with IgT/IgZ having the primary activity in fish mucosal immunity (Xu *et al*., 2013; Sunyer, 2013; Xia *et al*., 2016; Reverter *et al*., 2018; Pietrzak *et al*., 2020). C-reactive proteins are protein molecules in epidermal mucus extracellular vesicles that play an important role in innate immune defence. C-reactive proteins are formed as a reaction from infection, injury, and inflammatory processes. High levels of C-reactive proteins show inflammation in the body. C-reactive proteins play roles in repairing damaged tissues (Easy and Ross, 2010). Stressed fish have higher C-reactive protein levels than normal (Magnadóttir *et al*., 2019).

Other molecules involved in the innate immune activity are glycoproteins such as transferrin (Easy *et al*., 2012). Transferrin is an iron-binding glycoprotein that plays a role in iron transportation (absorption, storage, disposal) in fish epidermal mucus.

Therefore, transferrin plays an important role in the innate defence mechanism by binding to iron and reducing its availability from pathogens by chelating it. Transferrin's activity help resists pathogenic growth until the emergence of the immune system response (Dash *et al*., 2018). Catfish mucus contains mucins whose major component is glycoproteins. Mucins in mucus serve (i) to coat the surface of epithelial tissue, (ii) as a lubricant and protector, (iii) prevents parasitic, bacterial and fungal colonization, (iv) becomes the first line of defence against water friction and pathogenic invasion (Abdel-Shafi *et al*., 2019). Fish epidermal mucus also contains antibacterial peptides that function to modulate the function of B lymphocyte cells that play an essential role in the innate immune system (Reverter *et al*., 2018). Epidermal mucus and its components from various fish species can be a source of new antimicrobial agents and are involved in the innate immune system in fish (Table 1).

Table 1. Summary of epidermal mucus bioactivity as a tool of evaluating the health status of several fish species

Bioactivity	Bioactive molecules are involved in immune and/or stress responses	Stressors	Source organism	References
Mucosal barrier	Lectin, alkaline phosphatase, lysozyme	Parasitic infection	*Ctenophryngodon idella, Hypophthalmichthys moiltrix, Labeo rohita, Cirrhinus mrigala, Catla catla, Cyprinus carpio*	Abbas *et al*. (2020)
	Sialic acid (N-acetylneuraminic acid)	Exposed to zinc	Rainbow trout (*Salmo gairdneri* RICHARDSON)	Eddy & Fraser (1982)
Antibacterial activity	Glycoprotein	Bacteria infection	African catfish (*Clarias gariepinus*)	Abdel-Shafi *et al*. (2019)
	Peroxidase, IgM, protease	Feed deprivation	Gilthead Seabream (*Sparus aurata*)	Albaladejo-riad *et al*. (2020)
	Antibacterial Peptides	*Escherichia coli*	Yellow Fish Skin (*Pelteobagrus fulvidraco*)	Fakih & Dewi (2020)
	NK-lysin	*Aeromonas salmonicida*, *Vibrio anguillarum*	*Salmo salar*	Valero *et al*. (2019)
	Complement C1qC	*Escherichia coli*.	Siberian sturgeon (*Acipenser baerii*)	Fan *et al*. (2015)
	Complement C7	*Aeromonas hydrophila*	Grass carp	Shen *et al*. (2012)
	The antimicrobial peptide, Chrysophsins	-	*Dicentrarchus labrax*	Fekih-Zaghbib *et al*. (2013)
	Glycoproteins	-	Mudskipper (*Boleophthalmus pectinirostris*)	H. han Liu *et al*. (2019)
	Proteinaceous compounds	-	Mudskipper *Periophthalmodon schlosseri* (Pallas, 1770)	Mahadevan *et al*. (2019)
	Antimicrobial peptides	*B. subtilis, S. aureus, E. coli, P. aeruginosa*	*Puntius sophore*	M. Patel *et al*. (2020)
	Antimicrobial polypeptides, piscidins	Acute stress	Marine sea bass (*Dicentrarchus labrax*)	Terova *et al*. (2011)
	Lysozyme, protease, alkaline phosphatase, esterase	*Yersinia ruckeri*	Rainbow trout (*Oncorhynchus mykiss*)	Sheikhzadeh *et al*. (2012)
	Peptides	*Salmonella enterica C610*	Arctic char (*Salvelinus alpinus*), brook trout (*S. fontinalis*), koi carp (*Cyprinus carpio* sub sp.	Subramanian *et al*. (2008)

			koi), striped bass *(Morone saxatilis)*, haddock *(Melanogrammus aeglefinus)*, hagfish *(Myxine glutinosa)*	
	Grammistin	-	Soapfish *(Grammistes sexlineatus)*	Sugiyama *et al.* (2005)
Mucosal cellular innate immunity	Lysozyme, alkaline phosphatase proteases	Effects of season and fish size	Rainbow trout, *(Oncorhynchus mykiss)*	Abolfathi *et al.* (2020)
	Peroxidase, IgM, protease	Feed deprivation	Gilthead Seabream *(Sparus aurata)*	Albaladejo-riad *et al.* (2020)
	Terminal carbohydrates, protease, antiprotease, peroxidase, lysozyme, IgM	Skin ulcers	Gilthead seabream *(Sparus aurata)*	Tapia-Paniagua *et al.* (2018)
	Lysozyme, peroxidase	-	*Oreochromis niloticus*	Srichaiyo *et al.* (2020)
	C-Reactive protein, lysozyme	Sewage chemicals	Common carp *(Cyprinus carpio* L.)	Tarnawska *et al.* (2019)
	Trypsin	Environmental influence	Atlantic salmon *(Salmo salar* L.)	Braun *et al.* (1990)
	Peroxidase	Exposed to cadmium	*Cyprinus carpio* L.	Brokken *et al*, (1998)
	Alkaline phosphatase, cathepsin B, lysozyme, cortisol	Short-term stress, Long-term stress	Atlantic salmon *(Salmo salar* L.)	Easy & Ross (2010)
	Transferrin	-	Atlantic cod *(Gadus morhua)*	Easy *et al.* (2012)
	Lysozyme	Smoltification	Atlantic salmon *(Salmo salar)*	Fagan *et al.* (2003)
	Lysozyme	Salt concentration	*Cyprinus carpio*	Ghalambor *et al.* (2020)
	Protein, alkaline phosphatase, myeloperoxidase, lysozyme	*Aeromonas hydrophila* infection	*Oreochromis mossambicus*	Gobi *et al.* (2018)
	Terminal carbohydrates (N-acetylneuraminic acid, mannose, fucose and N-acetylgalactosamine), proteases, lysozyme, peroxidase, alkaline phosphatase, esterases, ceruloplasmin	*Micrococcus lysodeikticus* infection	Senegalese sole *(Solea senegalensis,* Kaup)	Guardiola *et al.* (2017)
	Protease, peroxidase	Acute crowding, anaesthetic agents, air exposure	*Sparus aurata* L.	Guardiola *et al.* (2016)
	Lectin, terminal carbohydrate	Heavy metals (As, Cd, Hg)	*Sparus aurata* L.	Guardiola *et al.* (2015)
	Peroxidase	Thermal pollution	*Oncorhynhcus mykiss*	Iger *et al.* (1994)
	Alkaline phosphatase, lysozyme, protease, lectin	Brackishwater polyculture	*Lates calcarifer, Chanos chanos, Mugil cephalus*	Kumar *et al.* (2019)
	Alkaline phosphatase	Environment, nutrition	Various species of fish	Lallès (2019)
	Glycoprotein	-	Mudskipper (*Boleophthalmus pectinirostris*)	H. han Liu *et al.* (2019)
	Lysozyme	Short-Term feed deprivation	Channel catfish (*Ictalurus punctatus*)	L. Liu *et al.* (2013)
	Peptidylarginine deiminase, complement component C3, C-reactive proteins	-	Cod (*Gadus morhua* L.)	Magnadóttir *et al.* (2019)
	Lysozyme, protease, alkaline phosphatase, esterase, transferrin, IgM	*Micrococcus lysodeikticus* infection	Olive flounder (*Paralichthys olivaceus*)	Palaksha *et al.* (2008)

	Proteomic profile: Calmodulin, cystatin-B, histone H2B, peroxiredoxin1, apolipoprotein A1, natterin-2, 14-3-3 protein, alfa enolase, pentraxin, warm temperature acclimation 65 kDa (WAP65kDa) and heat shock proteins	Pathogens and external stressors	Lumpsucker (*Cyclopterus lumpus*)	Patel & Brinchmann (2017)
	Acute-phase protein, antimicrobial proteins, cytokines, lectin, lysozymes, mucin, peroxidase, proteases, oxidoreductase	-	*Cyprinus carpio*	Pietrzak *et al*. (2020)
	Calpain small subunit 1, glutathione-S-transferase omega 1, proteasome 26S subunit, 14-kDa apolipoprotein, beta 2-tubulin, cold-inducible RNA binding protein, malate dehydrogenase 2 (mitochondrial) and type II keratin	*Vibrio anguillarum*	Atlantic cod (*Gadus morhua*)	Rajan *et al*. (2013)
	Protease, cortisol	*Sea lice*	*Salmo salar*	Ross *et al*. (2000)
	Actins, keratins, glycolytic enzymes, ubiquitin, heat shock proteins, transferrin, hemopexins	-	*Sparus aurata*	Sanahuja & Ibarz (2015)
	Lysozyme, protease, carboxylesterase, alkaline phosphatase, acid phosphatase, catalase, peroxidase,	-	Indian major carp (*Labeo rohita*)	Srivastava *et al*. (2018)
	Lysozyme, proteases, cathepsin B; alkaline phosphatase	-	Arctic char (*Salvelinus alpinus*), brook trout (*S. fontinalis*), koi carp (*Cyprinus carpio*), striped bass (*Morone saxatilis*), haddock, (*Melanogrammus aeglefinus*), Atlantic cod (*Gadus morhua*), hagfish (*Myxine glutinosa*).	Subramanian *et al*. (2007)
	Lysozyme, alkaline phosphatase, esterase, protease, protein	-	*Clarias gariepinus, Channa micropeltes, Channa striatus, Oxyeleotris marmorata, Oreochromis niloticus, Hemibagrus nemurus*	Timalata *et al*. (2015)
	Lysozyme, peroxidase, alternative complement (ACH50)	*Streptococcus agalactiae*	*Oreochromis niloticus*	Van Doan *et al*. (2019)
	Lysozyme, protease, anti-protease, cathepsin B, alkaline phosphatase, peroxidase)	*Aeromonas hydrophila, Vibrio parahaemolyticus*	*Amphiprion clarkii*	Wang *et al*. (2019)
	IgZ	*Aeromonas hydrophila*	Blunt snout bream (*Megalabrama amblycephala*)	Xia *et al*. (2016)
	Lectins, complement components, antibacterial peptides, immunoglobins, structural proteins	*Edwardsiella ictaluri*	Yellow catfish (*Pelteobagrus fulvidraco*)	Xiong *et al*. (2020)
Biomarker of oxidative stress	F2-isoprostanes	Waste pollution	*Esox lucius, Salvelinus namaycush*	Bulloch *et al*. (2020)
	Metallothioneins, HSP70	Sewage chemicals	Common carp (*Cyprinus carpio* L.)	Tarnawska *et al*. (2019)
	O_2•, H_2O_2, TBARS (thiobarbituric acid reactive substances), carbonyl proteins, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), vitellogenin (VTG) and metallothionein (MT)	Metals and PAHs	Blackfin goodeid (*Girardinichthys viviparus*)	Dzul-Caamal *et al*. (2016a)

	O_2•, H_2O_2, TBARS, carbonyl proteins, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), vitellogenin (VTG) and metallothionein (MT)	Exposed to crude oil	*Goodea gracilis*	Dzul-Caamal, *et al*. (2016b)
	Reactive oxygen species (ROS), reactive nitrogen species (RNS), antioxidant parameters of superoxide dismutase (SOD), glutathione peroxidase (GPx)	*Aeromonas hydrophila* infection	*Oreochromis mossambicus*	Gobi *et al*. (2018)
	Carboxylesterase	Organophosphate exposure	*Cirrhinus mrigala*	Nigam *et al*. (2014)
	Total antioxidant capacity, total oxidative status, esterase, cortisol	Gold nanoparticles	*Sparus aurata* L.	Oliveira *et al*. (2018)
Modulate the immune system and bioactive carrier	Protein-based nanoparticles	-	*Lophiosilurus alexandri*	Charlie-Silva *et al*. (2019)
Mucosal humoral immunity	IgM	Effect of freezing and lyophilization	Gilthead seabream (*Sparus aurata*)	Cordero *et al*. (2016)
	IgM	*Vibrio harveyi*, *Vibrio angillarum*, *Photobacterium damselae*, *Escherichia coli*, *Bacillus subtilis*, *Shewanella putrefaciens)*	Gilthead seabream (*Sparus aurata*), European sea bass (*Dicentrarchus labrax*), shi drum (*Umbrina cirrosa*), common dentex (*Dentex dentex*), dusky grouper (*Epinephelus marginatus*)	Guardiola *et al*. (2014)
	IgM	Acute crowding, anaesthetic agents, air exposure	*Sparus aurata* L.	Guardiola *et al*. (2016)
Biomarker of stress	Glucose, lactate, protein, cortisol	Hypoxia and netting	Meagre *(Argyrosomus regius)*	Fernández-Alacid *et al*. (2019)
	Glucose, lactate, protein, cortisol	Fish capture, bacterial infection, fasting	Meagre, sea bass, sea bream	Fernández-Alacid *et al*. (2018)
	Cortisol, *muc-2* gene expression	Handling, density, temperature, fasting	Greater amberjack (*Seriola dumerili*)	Fernández-Montero *et al*. (2020)
	Cortisol	Acute crowding, anaesthetic agents, air exposure	*Sparus aurata* L.	Guardiola *et al*. (2016)
	Cholinesterase	Organophosphate exposure	*Cirrhinus mrigala, Labeo rohita,Catla catla*	Nigam *et al*. (2014)
	Lysozyme, IgM, alkaline phosphatase, protein total	Lead pollution	*Neogobius melanostomus*	Omidi *et al*. (2020)
	Cortisol, glucose, lactate	MS-222 exposure	*Symphysodon aequifasciata*	Ouyang *et al*. (2020)
	Cytokeratins	Chronic stress	*Sparus aurata* L.	Pérez-Sánchez *et al*. (2017)
Biomarker of endocrine disruptor	Vitellogenin, zona radiata protein	Waterborne nonylphenol	*Salmo salar* L.	Meucci & Arukwe (2005)

Epidermal mucus bioactivity as antimicrobial

Fish epidermal mucus contains antimicrobial peptides, which is one of the primary molecules to fight pathogenic microbial invasions (Cipolari *et al*., 2020). Antimicrobial peptides are endogenous peptides with short-chain, cationic, amphipathic, and molecular weight less than 13 kDa. Antimicrobial peptides are a component of the innate immune system found on the surface layer of cytolytic and microbicidal epithelial tissues. These peptides generally consist of 10 to 50 amino acids with 2 to 8 positive charges and have various activities, including inhibiting microbial growth of Gram-positive and Gram-negative bacteria, fungi, viruses, and parasites (Lei *et al*., 2019). Antimicrobial peptides are key components of the innate immune system that acts as the first line of defence against various pathogenic microbial invasion without having high specificity or memory. Other biological activities of antimicrobial peptides are immunocompetence and homeostasis (Chaturvedi *et al*., 2020), as well as an immunomodulator to enhance body immunity (Gokhale and Satyanarayanajois, 2014). The types of antimicrobial peptides found are (i) α-helical peptides piscidins (moronecidins, pleurocidins, dicentracins, and chrysopsins, (ii) linear peptides such as pardaxin and pelteobagrin, (iii) defensin namely cysteine-rich antibacterial peptides, (iv) grammistins (v) cathelicidins (vi) histone-like proteins (Reverter *et al*. 2018; Cipolari *et al*., 2020; Chaturvedi *et al*., 2020). Antimicrobial peptides are derived from biologically inactive proteins that are processed to the active forms and derived from functional proteins (Reverter *et al*., 2018). The expression of antimicrobial peptides induced by molecular patterns associated with pathogens and molecular patterns associated with damage (Chaturvedi *et al*., 2020). The mechanism of antimicrobial action of these peptide molecules is done by crossing the cell membrane, interacting with microbial DNA, thus disrupting transcription and/or replication (Dash *et al*., 2018; Chaturvedi *et al*., 2020). Peptides in the epidermal mucus of *Clarias gariepinus* have functioned as an antibacterial by preventing the colonization of Gram-positive and Gram-negative pathogens. Peptides also contain secretin/glucagon neuropeptides that have an immune response to acute bacterial infections (Abdel-Shafi *et al*., 2019). Other antibacterial proteins found in fish mucus are L-amino acid oxidases, ribosomal proteins such as L40, L36A, L35, and S30, and protein such as haemoglobin (Hb-β) (Reverter et al., 2018).

Commensalism microbiota in fish epidermal mucus plays an important role in controlling opportunistic pathogens. Recent studies have shown specific mechanisms by which the host can recognize commensal bacteria, and their metabolites can control the proliferation of pathogenic bacteria. For example, Reverter *et al*. (2018) explain that the bacterium *Flectobacillus major* from the mucous layer of the rainbow trout skin produces sphingolipids which induce the production of immunoglobulin T (IgT), forming B lymphocyte cells and antibody responses, to control the growth of pathogenic bacteria. Another study found special metabolites that have antibacterial and antifungal activities in bacterial strains isolated from fish mucus, so it can control the development of host pathogenic bacteria.

Biochemical biomarkers in fish epidermal mucus as a stress response

Stress can decrease the immune system, reducing resistance to pathogenic invasions, and threatening the survival of fish. In stressful situations, there is a relationship between the endocrine system and the immune system, e.g. cytokine and neuropeptide role in the neuroendocrine and immune systems. Thus, the study of the interaction between the endocrine system and the immune system in fish mucosa, after its exposure to stress, continues to develop as an alternative in non-invasive early detection efforts (Guardiola *et al*., 2016).

The fish mucosal immune system comprises innate and adaptive immune cells that are arranged exclusively and work together to protect the host against pathogenic invasions. One of them is SALT. The skin as the first line of defence can respond to stress agents after activation of receptors on epidermal cells. The epidermal mucus on fish skin acts as a storage/reservoir of various immune components that block various kinds of chemical, physical, and biological stressors (Easy and Ross, 2010; Guardiola *et al*., 2016). Stressor agents also trigger the production of steroid hormones (e.g. cortisol) which are detected in epidermal mucus as biochemical biomarkers. Primary, secondary, and tertiary effects on stress-affected fish have the potential as biochemical biomarkers. The primary effect that occurs is elevated levels of plasma cortisol and catecholamine. Elevated levels of plasma glucose and lactic acid, respiratory stimulation, and increased oxygen intake are the secondary effects, whereas decreased growth, decreased reproduction, and immunosuppression are the tertiary effects of stress-affected fish. Peroxidase enzyme activity occurs as a non-specific stress response in fish exposed to cadmium (Brokken *et al*., 1998). The stress on *Salmo salar* L. because of *Lepeophtheirus salmonis* infection leads to the release of innate immune factors (protease enzymes, actin proteins, transferrin) and cortisol into the serum and the epidermal mucus to eliminate the effects of stressors (Easy and Ross, 2010). According to Easy and Ross (2010) there are changes in the activity of the alkaline phosphatase, cathepsin B, lysozyme and protease enzymes in Atlantic salmon (*Salmo salar* L.) mucus due to long-term stress handler and there is a positive correlation between the profile of the enzyme with the hormone cortisol. Guardiola *et al*. (2016) have examined the levels of epidermal mucus cortisol of *Sparus aurata* L. as a reliable non-invasive acute-stress biomarker. Besides cortisol, immunoglobulin M, protease enzymes activity and peroxidase enzymes are elevated levels in the stress-affected fish epidermal mucus. Cortisol, produced by the adrenal glands are lipophilic, which can diffuse through the cell membranes to reach several target tissues including secreted into the epidermal mucus. Therefore, measurement of cortisol levels as a biochemical biomarker in epidermal mucus is a non-invasive method to test stress or health status of fish. The study contributes a better understanding of the potential of epidermal mucus as a biochemical biomarker for early detection of stress.

Epidermal mucus of stress-affected fish due to hypoxia and crowding contain structural protein molecules (glycoprotein, lectin, actin, transferrin) and enzymes that serve as the body's defence and metabolism system (Fernández-Alacid *et al*., 2019). Mucus contains glucose metabolites and cortisol hormone (Guardiola *et al*., 2016) which positively correlated with plasma cortisol levels, thus potentially as a biochemical biomarker with a non-invasive, fast, and simple method (Fernández-Alacid *et al*., 2018) to detect early stress response and disease (Fernández-Alacid *et al*., 2019). Other metabolites found in stress-affected fish mucus are lactic acid and proteins. Lactic acid levels and the ratio of glucose to proteins can be used as stress biomarkers due to environmental stress (Fernández-Alacid *et al*., 2018).

Fish skin is the key target of oxidative stress because of the production of Reactive Oxygen Species (ROS) resulting from heavy metal pollution and polycyclic aromatic hydrocarbons in aquatic ecosystems. We believe oxidative stress to be a pathway for the mechanism of toxicity in fish exposed to environmental contaminants. Epidermal mucus is a biological matrix suitable for analyzing biochemical responses that occur because of oxidative stress. For the first time, Dzul-Caamal *et al*. (2016) have proven the benefits of the epidermal mucous layer as a bio-indicator of oxidative stress using biochemical biomarker panels such as $O2^{\bullet}$, H_2O_2, lipid peroxidation (as TBARS), carbonyl proteins (RC=O), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), vitellogenin (VTG) and metallothionein (MT) to monitor the health status of protected wild fish namely *Girardinichthys viviparus* in two polluted lakes in the Mexican Valley. The biochemical biomarker panel is also used to monitor the health of the rare *Goodea gracilis* fish (Hubbs and Turner, 1939) exposed to polycyclic aromatic hydrocarbons from crude oil spills (Dzul-Caamal *et al*., 2016). Exposure to these pollutants induces the production of reactive oxygen compounds and elicits antioxidant defence responses detected in the epidermal mucous layer. For the first time, the results of this research have proven the benefits of epidermal mucus as an ecotoxicological biomonitoring tool for monitoring the health status of endemic fish. F2-isoprostanes (F2-isoPs) is also a reliable biochemical biomarker for oxidative stress responses in *Salvelinus namaycush* exposed to heavy metal pollutants. The levels of these compounds are measured in the liver and plasma, which could kill the fish, but because of social pressure and environmental conservation, a non-invasive method using fish epidermal mucus is used to analyze oxidative stress biomarkers (Bulloch *et al*., 2020). Fernández-Montero *et al*. (2020) stated that there is a positive correlation between plasma cortisol levels and cortisol levels in the epidermal mucus of *Seriola dumili* that were stressed due to temperature factors, stress management, and fasting. *muc*-2 gene expression occurs as a biomarker of epidermal mucus production.

Prospects of epidermal mucus as a fish health evaluation tool

The study of fish mucus as a potential biological matrix to evaluate stress and health status of fish due to pathogen invasion and environmental stress has lately increased. Potential fish mucus to be developed as a fish health evaluation tool and bioactive components in the mucus is very diverse so that it has the potential as a natural medicinal ingredient. Several studies in Indonesia that have been conducted are the application of immunocytochemical Streptavidin Biotin (SB) test on the epidermal mucus of the tiger grouper (*Epinephelus fuscoguttatus*) as an early diagnostic test for *viral nervous necrosis* (VNN) disease. The fast and accurate SB test is suitable to be applied in routine biomonitoring and VNN prevention programs in the Indonesian Fish Quarantine because it can be done without killing the fish, scientifically accepted, and does not pollute the environment (Sudaryatma *et al*., 2012). Epidermal mucus of striped snakehead (*Channa striata*) in gel formulation is used to treat burns in rabbits (*Oryctolagus cuniculus*) (Safaruddin *et al*., 2019; Rusli and Yeniati, 2019). Epidermal mucus of Indonesian shortfin eel (*Anguilla bicolor*) is also a potential candidate for healing burns (Abi *et al*., 2019). However, protein molecules and their profile which acts as wound healing factors have not been studied. The study of Fakih and Dewi (2020) with In silico computational method successfully simulates the potential of epidermal mucus as a source of antimicrobial peptides, which serves as the first line of defence in humans against pathogenic bacteria, such as *Escherichia coli*. Some antimicrobial peptides isolated from the skin mucus of yellow catfish (*Pelteobagrus fulvidraco*) can inhibit Penicillin-Binding Protein 3 (PBP3) in *Escherichia coli*, including Pelteobagrin, Myxinidin, Pleurocidin, and Pardaxin-P1. These antimicrobial peptides can be selected as a natural antimicrobial candidate, even though the study is modelling. In Indonesia, studies on the detection and isolation of antimicrobial peptides, structural proteins and enzymes from fish mucus are still scarce, because of the lack of concern to its antimicrobial potential and its involvement in the mucosal defence system.

The prospect of proteomics studies on the biological epidermal mucus activity needs to be encouraged, given the diversity of fish biodiversity that has the potential to produce bioactive components and metabolites that are involved in the mucosal and antimicrobial immune systems specifically. Research with the proteomics approach is expected to successfully identify new proteins that play a role in innate immunity. Previous studies have not known about protein profiles, so knowledge about its bioactivity is very limited. Proteomics data provide information about protein profiles, which will bring a comprehensive understanding of the function and the biological activity of fish skin mucus in fighting stress and microbial infections. Proteins identified in the mucus are useful for fish stress and health status (Fæste *et al*., 2020; Xiong *et al*., 2020; Dang *et al*. 2020). Opportunities for future studies are wide open to develop the potential of fish mucus as a candidate for natural antimicrobials and stress biomarkers. Study collaboration opportunities focus on proteomics studies aimed at discovering new bioactive protein molecules and their profiles isolated from native Indonesian fish. It's because the potential of fish is not only as a source of nutrients, but also as a source of structural proteins and enzymes involved in the mucosal immune system, a source of antimicrobial peptides, and a source of anti-inflammatory. Antimicrobial peptides derived from fish mucus have broad-spectrum bioactivities, which play roles in cellular communication, as modulators, mediators, hormones, effectors, cofactors, activators, and stimulators. Recent studies on the pharmacological effects of fish peptides show antihypertensive, immunomodulatory, antioxidant, antitumor, and antimicrobial activities, resulting in potentially exciting ingredients for diagnostics, therapy, and treatment for humans and animals (Cipolari *et al*., 2020; Fæste *et al*., 2020). Besides studies on proteomics, the studies of the influence of variations in environmental factors on the production and function of mucus are crucial to its function as a biological barrier and its role in mucosal immunity. According to Cabillon and Lazado (2019), changes in environmental factors, not only affect the phenotype of the mucous layer structures and molecular responses but also affect the bioactive components of the mucus and the structure of the microbiota lining the surface of the mucosa. It's important to consider the effect of various environmental factors on adaptative mechanisms in the production of mucus. A comprehensive understanding of mucosal structures and long-term adaptation mechanisms in response to environmental changes is indispensable in modern aquaculture production technology with strict control over environmental changes for increased biosecurity and sustainable production systems.

CONCLUSION

Fish epidermal mucus contains bioactive components such as structural proteins, enzymes, antimicrobial proteins and peptides that have the potentials (i) as antibacterial, antiviral, antifungal and antiparasitic agents and the potential to be developed as new materials for diagnostic, therapeutic or treatment agents in humans and animals; (ii) as the development of non-invasive, non-lethal methods for early detection of infections and stress; (iii) as a biological matrix for analyzing biomarkers for oxidative stress because of environmental pollutants. Not only is epidermal mucus a potential biological matrix for assessing fish's immune and health status, but it also acts as a bio-indicator of stress by detecting biochemical biomarkers that emerge.

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