Principles and Methods of Counteracting Harmful Salmon–Arthropod Interactions in Salmon Farming: Addressing Possibilities, Limitations, and Future Options

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The arthropod salmon louse (Lepeophtheirus salmonis) is a major threat to Atlantic salmon aquaculture and wild salmonids. Essentially like in monoculture, very high concentrations of susceptible hosts may result in high reproduction and severe production of waves of pests. Pest management is crucial both for fish health and protection of wild fish populations from aquaculture influence. Various methods have been utilized to control salmon lice infestations, such as pesticide use, physical treatments, construction modifications, fallowing, breeding, vaccination, and biological control. Most of the methods are partially successful, but none completely fulfills the necessary pest control strategy. Like in agriculture, lice/pest management is an arms race, but the marine environment makes it even more difficult to precisely hit the target pest and avoid unintended negative effects on general wildlife. In this study, we provide an overview of the methods and principles of salmon lice management and address current possibilities and limitations. We also highlight the potential of emerging strategies and enabling technologies, like genome editing, RNA interference, and machine learning, in arthropod management in aquaculture.

Keywords: enabling technologies, genome editing, marine arthropod, salmon lice, delousing, medical treatments, non-medical treatments

INTRODUCTION

Human population is projected to increase to 11.2 billion by the end of the century, and the buying power is expected to continue to increase (UN Economic & Social Affairs, 2019). These increases will drive the need for human food, and scarcity is expected to be a great challenge for humans in the coming century (FAO, 2020a). The cultivable land needed for agriculture is decreasing and the future of food production is likely in the marine environment. At least one-third of agricultural output is currently lost due to damage caused by pests and diseases (Oerke et al., 2012). Arthropods,
by far the largest invertebrate phylum that include approximately eighty percent of all animal species inhabiting the earth (Zhang, 2013; Ghafor, 2020), cause a main problem. Agricultural losses due to arthropods are enormous (Bradshaw et al., 2016), and major attention has been paid to the study of terrestrial arthropods. Comparatively, the marine arthropods and parasites have received less attention.

Over the last 70 years, global fish and seafood production has been a success story and the production has increased sevenfold (FAO, 2020b). The production value of the Atlantic salmon and other salmonids added up to 13.1 billion euros in 2018. Vaccination programs and best practice in cultivation have resulted in a drastic reduction in disease outbreaks as well as in medical treatments. The use of antibiotics in salmon farming in Norway alone has, for example, been reduced from approximately 2.13 µg/kg fish in 2006 to 0.14 µg/kg fish in 2019 (Directorate of Fisheries, 2020; Norwegian Institute of Public Health, 2020) mainly due to mass vaccination of juvenile salmonids. During these years, the use of antibiotics has also been drastically reduced in Scotland and Canada (Love et al., 2020). Pest control still represents, however, a major challenge and limits the growth potential of the salmon industry. As in terrestrial agriculture, the cost of arthropods to the salmon industry is very high. Salmon lice (Lepeophtheirus salmonis) are a major threat to both farmed and wild Atlantic salmon in the North Atlantic region (Costello, 2006; Torrissen et al., 2013), and Caligus rogercresseyi is considered a major threat to salmon in Chile (Gonzalez et al., 2000; Gonzalez et al., 2015). L. salmonis is known to have two allopatric subspecies, L. salmonis salmonis from the Atlantic and L. salmonis oncorynchii from the pacific, each having biological, morphological, and genetic differences (Skern-Mauritzen et al., 2014). The financial losses caused by lice infestation amount to about 9% of overall production revenue (Abolofia et al., 2017). The first-hand value of salmon in 2019 was approx. 6 billion euro in Norway (SSB, 2020), whereas in Scotland it was valued at approx. 1.2 billion euro (Munro, 2020). The expenses for combating salmon lice in the Norwegian salmon industry was estimated to be around 500 million euro (Iversen et al., 2019), 17 million euro in Canada, 304 million euro in Chile, and 78 million euro in Scotland in 2019 (Just Economics, 2021). Salmon lice limit the further growth of the salmon aquaculture industry.

In this study, we present a broad overview of current scientific advances as well as methods and principles employed to combat this significant marine parasite (Figure 1).

**History**

The Norwegian-Danish Bishop Erik L. Pontoppidan first described the salmon lice in a text, stating that the salmon had partly returned from the sea to freshwater to get rid of greenish vermin by rubbing and washing in the rapid stream of waterfalls (Pontoppidan, 1755; see Torrissen et al., 2013). Salmon louse was later classified by the Danish zoologist Henrik Nikolai Krøyer as Lepeophtheirus salmonis in 1837 (Krøyer, 1837; IMR, 2009). Severe infestation of sea lice on fish, causing fish deaths in Canada, was described in a 1940 report (White, 1940; see Torrissen et al., 2013). In the early 1970s, Harald Skjervold and Trygve Gjedrem developed modern principles for the breeding of the Atlantic salmon and pioneered an important industry in Norway (Syrstad, 2009). The first outbreak of sea lice in aquaculture facilities was reported in the 1960s (Misund, 2018).

It is therefore worth noting that salmon lice were present in salmon populations as a natural parasite long before aquaculture. Adverse reactions of salmon lice to other salmonid and to wild salmon were recorded for the first time in 1992. The later industrialized farming of salmon increased the number of hosts, which in turn increased the number of lice and, subsequently, the infection rate of both farmed salmon and wild salmonids (Heuch and Mo, 2001). The number of salmonids in fish pens in Norway has risen from approximately 9.5 million in 1994 to 445 million in 2019, according to data from the Norwegian Directorate of Fisheries. Chile is the world’s second largest producer of salmon after Norway, accounting for 30% of total farmed salmon production (FAO, 2019). Salmonid industry is also booming in the United Kingdom and Canada, and the number is rapidly increasing.

**Impact of Salmon Lice**

The salmon louse is a salmonid parasite specialized on host fish of the three genera *Salmo*, *Salvelinus*, and *Oncorhynchus* (Wootten et al., 1982). Salmon lice have a significant effect on salmonids during the marine part of their life cycle since they feed on fish mucus, blood, and epidermal tissues (Costello, 2006). The effects of these parasites on fish include physiological stress, growth reduction, immune system suppression, and osmoregulation imbalance (Johnson et al., 2004; Costello, 2006). Higher rates of infestation lead to skin lesions, secondary microbial and viral infections, and, ultimately, increased mortality in the absence of treatment (Grimmes and Jakobsen, 1996; Pike and Wadsworth, 1999). The infestation of salmon lice has a huge economic impact on the aquaculture industry and is projected to escalate further in the coming years (Liu and Bjelland, 2014). In Norway, salmon lice levels are regulated by law in order to protect wild salmon (traffic light system) (Fiskeridepartementet, 2015), and this increases the intensity of treatment and handling, which drives up costs and causes fish welfare issues. Increased cost of production due to salmon lice come from medical and non-medical treatments, cleaner fish, net cleaning, stress and increased mortality, reduced weight gain, fish handling costs, and higher ratios of feed consumption (Iversen et al., 2018, 2019). Salmon lice may also be reservoirs of fish pathogens (Gonçalves et al., 2020).

**Control of Salmon Lice**

Control of salmon lice includes non-medical approaches and medical delousing. Non-medical approaches are divided into preventive and physical delousing methods. Due to its consistency and efficacy, the most common delousing method is medical treatments (Aaen et al., 2015). Attempts to develop resistant fish and vaccines against salmon lice have also been reported (Kaur et al., 2015; Contreras et al., 2020; Swain et al., 2020). Regulatory authorities in salmon-producing nations have established mandatory and maximum thresholds on the number of mature or motile lice per farmed fish at production sites to limit the transmission of sea lice and sea-lice larvae from farming.
facilities to wild salmon smolts. There is a legal limit in Norway for the maximum mean number of lice per farmed salmon, as well as obligatory reporting of lice numbers to authorities and delousing if the limit is exceeded (Heuch et al., 2005). The regulatory requirement of lice abundance threshold in various locations is summarized in Table 1.

**MEDICAL METHODS**

**Medical Treatment and Resistance**

Medical treatment has been widely used to combat the problem of sea lice, as it is the most productive and predictable measure (Aaen et al., 2015). In 1974, Norway began treatment of sea lice with the use of organophosphate metrifonate, followed by Scotland in 1979, Chile in 1981, and Canada and Faroe Islands in the mid to late 1990s (Grave et al., 2004; Aaen et al., 2015). Since then, different forms of chemicals have been used as bath treatments, e.g., organophosphates, pyrethroids and hydrogen peroxide, and as feed additives, e.g., emamectin benzoate and benzoyl urea (Table 2) (Burridge et al., 2010; Aaen et al., 2015). The cost of medication is relatively high and was estimated to be in the range of 1–2 billion NOK (100–200 million euro) in 2014 (Iversen et al., 2018), excluding the costs of Chile, the United Kingdom, Canada, Ireland, Faroe Islands, and the United States.

The extensive use of chemical agents to combat sea lice has led to an inevitable drift toward drug-resistant parasites (Aaen et al., 2015). Successful treatment of the pest depends on the doses administered. For parasites like sea lice, the dosage is also determined by the host’s ability to tolerate the toxicity of the agent. A smaller reduction in dosage may reduce the effect on parasites and generate resistance driven by natural selection in pests (Kunz and Kemp, 1994). Various genetic resistance mechanisms, such as point mutation in a target gene, upregulation of detoxification metabolism and efflux pumps in the intestines of parasites, changes in the thickness of the cuticle and other mechanisms to reduce chemical penetration, have been documented in arthropods (Brattsten et al., 1986; Aaen et al., 2015).

Resistance to a number of commonly used delousing chemicals has been registered, as well as ineffective treatment with emamectin benzoate and pyrethroids since 2008 (Aaen et al., 2015; Grøntvedt et al., 2016; Fjørtoft et al., 2020). Treatment failure and low treatment efficacy with azamethiphos, first noted in 2009 after re-introduction, is widespread along the coast (Kaur et al., 2015; Grøntvedt et al., 2016; Jensen et al., 2017). Losses of sensitivity to hydrogen peroxide is also reported (Helgesen et al., 2017). The number of prescriptions for medical treatment of sea lice is decreasing in recent years. Chemical agents are not prescribed when the efficacy of the treatment is low due to resistance. This could have contributed significantly to the decrease in prescription rates (Helgesen et al., 2017).

Chemical agents used against salmon lice might have negative effects on non-target species. Spillover from treatment around the fish farm could pose a significant risk to non-target organisms such as lobster (Olsvik et al., 2015), shrimp, and other crustacea and bivalves. Local treatments in the marine environment have limitations due to, for example, changing volume of water, addition of solvent to large volumes, and water currents, making precision difficult. Negative effects on many non-target species studied have been observed at lower concentration levels of chemotherapeutic agents than those used for salmon lice treatment (Macken et al., 2015; Urbina et al.,

| Country     | Lice limit (average)                                                                 | Number of fish | Frequency                                      | Sources                                      |
|-------------|--------------------------------------------------------------------------------------|----------------|-----------------------------------------------|---------------------------------------------|
| Norway      | 0.2 adult female lice per fish sensitive period* In Nordland, Troms, and Finnmark: week 21–26, otherwise week 16–22 | 10 per cage    | Weekly (4°C or above)                         | Ministry of Trade, Industry and Fisheries, 2013, 2017 |
|             | 0.5 lice adult female lice per fish during rest of year                               | 10 per cage    | Weekly or monthly, at least 50% cage over 2 weeks |                                             |
| Scotland    | 2 adult female lice per fish                                                          | 10 per cage    | Weekly                                        | Luthman et al., 2019; Scottish Statutory Instruments, 2021 |
| Canada      | 3 motile lice per fish at all times                                                   | 10 per cage    | Monthly                                       | Luthman et al., 2019                         |
| Ireland     | 0.5 adult female lice during sensitive period, 2 adult female lice outside sensitive period | 6 per site     | 14 inspections per year plus follow up if required | Jackson et al., 2013                        |
| Faroe Islands | 1.5 adult female lice                                                                         | 10 per cage    | Bi-weekly                                     | Gislason, 2018; Luthman et al., 2019         |
| Chile       | 1.5 adult female during winter, 3 motile lice per salmon at all times                   | 10 per cage    | Weekly                                        | Luthman et al., 2019                         |
| ASC Salmon Standard | 0.1 adult female lice during sensitive period for wild salmonids. | 10 per cage | Weekly or monthly, depending on wild stock populations in the proximity | Luthman et al., 2019 |

*Sensitive period: Wild salmonids migration.
### TABLE 2 | Chemicals, Vaccines, and Repellents used in salmon lice control, as well as the concerns associated with them.

| Groups/compounds          | Primary site of action/ MOA                                                                 | Resistance in salmon lice                                                                 | Resistance mechanism                                                                                     | Sources                                                  |
|---------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| **Ivermectin: Oral treatment** |                                                                                            |                                                                                         |                                                                                                          |                                                          |
| Emamectin benzoate        | Chloride channel (CC) activators                                                             | Prevalent, overexpression of metabolic enzymes, and downregulation of GABA-gated CC and neuronal acetylcholinesterase (AChE) receptors. | Reported in nematodes and arthropods. Target site insensitivity due to knockdown (KD) mutations. Metabolic resistance associated with cytochromes P450 (CYPs), carboxylesterases (CST) and glutathione-S-transferases (GST). Changes in glutamate- and histidine-gated ion channels. | Arena et al., 1995; Igboeli et al., 2012; Carmichael et al., 2013; Sutherland et al., 2015; Lam et al., 2020 |
| **Benzoyl ureas: Oral treatment** |                                                                                            |                                                                                         |                                                                                                          |                                                          |
| Diflubenzuron (DF)         | Chitin synthesis inhibitor (CSI)                                                              | Yes. Also, poor absorption of DF and TF from the digestive tract                        | Overexpression of CYPs. Mutation in the chitin synthase gene I (CHS1)                                    | Pimprikar and Georghiou, 1979; Olsvik et al., 2015; Douris et al., 2016; Poley et al., 2018 |
| Teeflubenzuron (TF)        |                                                                                            |                                                                                         |                                                                                                          |                                                          |
| Lufeneron (LF)            |                                                                                            |                                                                                         |                                                                                                          |                                                          |
| **Organophosphates: Bath treatment** |                                                                                            |                                                                                         |                                                                                                          |                                                          |
| Azamethiphos              | Acetylcholinesterase (AChE) inhibitor                                                        | Mutation in AChE coding gene: Phe362Tyr mutation                                          | In arthropods: AChE mutation, overexpression of metabolic enzymes                                        | Denholm et al., 2002; Kaur et al., 2015, 2017; Valenzuela-Munoz et al., 2015; Jensen et al., 2017; Helgesen et al., 2019 |
| Metriphonate              |                                                                                            |                                                                                         |                                                                                                          |                                                          |
| Dichlorvos                |                                                                                            |                                                                                         |                                                                                                          |                                                          |
| **Pyrethroids: Bath treatment** |                                                                                            |                                                                                         |                                                                                                          |                                                          |
| Deltamethrin              | Voltage-gated sodium channels (VGSC) modulator                                               | Prevalent. Deltamethrin: Mutations in mtDNA. No association with previously identified mutations in VGSC | Arthropods: Target site insensitivity due to KD mutations. Metabolic resistance associated with CYPs, CSTs, and GSTs. | Martinez-Torres et al., 1998; Hemingway and Ranson, 2000; Santolamazza et al., 2008; Soderlund, 2012; Tschesche et al., 2021 |
| Cypermethrin              |                                                                                            |                                                                                         |                                                                                                          |                                                          |
| **Hydrogen peroxide: Bath treatment** |                                                                                            |                                                                                         |                                                                                                          |                                                          |
|                           | Gas bubble formation in haemolymph, mechanical paralysis.                                     | Yes Reported in Norway and Scotland                                                      | Reported in bacteria and fungi. Bacterioferritin coma protein is important in H2O2 resistance.         | Aaen et al., 2015; Helgesen et al., 2015; Singh et al., 2017; Liu et al., 2019 |
| **Preventive medicine**   |                                                                                            |                                                                                         |                                                                                                          |                                                          |
| **Vaccines: Oral or Injectable** |                                                                                            |                                                                                         |                                                                                                          |                                                          |
|                           | Delivery method                                                                              | Availability                                                                             | Issues                                                                                                   |                                                          |
|                           | Vaccination of fish, oral, injectables, and immersion                                         | There is one commercially available injection anti-sea lice vaccine. (C. Roger Cressey: Providean Aquatec Sea Lice, Tecnovax) | Only injectable vaccines have satisfactory efficacy. Alternative delivery methods, effective adjuvants, and vaccine targets are required. Injection candidates have provided 31–56% reduction in adult females. | Latorre and Grosman, 2013; Leal et al., 2019; Contreras et al., 2020; Swain et al., 2020 (https://www.tecnovax.com.ar/productos/provideanaquatec-sea-lice) |

(Continued)
In vitro-synthesized mRNA-based vaccines combined with lipid nanoparticles have been the first to be approved against SARS-CoV-2 outbreak (Anderson et al., 2020; Mulligan et al., 2020). Although mRNA vaccines are not currently available in aquaculture, this brings hope for successful research and potential application in other areas where vaccines are needed, as well as vaccine research in general.

In aquaculture, the introduction of vaccines as a preventive method is a necessity for sustainable fish farming (Adams, 2019). From the experience of the viral and bacterial vaccines produced for salmon, we see how effective vaccines can be in aquaculture (Sommerset et al., 2005). However, cost-efficient vaccination against salmon lice remains an unsolved challenge. Vaccines against ectoparasites are still in their infancy, with a few successful commercial products providing reliable protection, such as against cattle tick (Willadsen et al., 1995). The complexity of interactions between vertebrate host and arthropod parasites is yet to be explored for potential vaccine targets (Raynard et al., 2002; Fuente et al., 2016). Translated research from advances in the tick vaccine have already provided promising results in peptide vaccines against salmon lice. Peptides from salmon lice were conjugated with T-cell epitopes (TCEs), that are universally immunogenic in mammalian systems (Panina-Bordignon et al., 1989; Leal et al., 2019). TCEs from tetanus toxin and measles virus are known to increase the immunogenicity in salmonid immune system (Leal et al., 2019; Contreras et al., 2020; Swain et al., 2020). Moreover, technologies, such as adjuvants and nanoparticles, in combination with conventional approaches for enhanced immunogenicity are additional perspectives for the future (Dadar et al., 2017; Angulo et al., 2020).

So far, there is only one commercial injectable vaccine available for sea lice, C. rogercresseyi namely Tecnovox’s Providean Aquatec Sea Lice. The vaccine was reported to have efficacy of 61–86% reduction of the number of post-challenge parasitic stages of lice in immunized trout (Latorre and Grosman, 2013). Only injectable vaccines have provided positive results, but they are far from optimal. While protection is generally high, application is labor-intensive and stressful for the fish (Angulo et al., 2020). However, with the introduction of high-throughput injectable devices capable of injecting thousands of fishes under anesthesia every hour, application time has been greatly reduced. Furthermore, additional efforts in salmon lice vaccine research could also be directed toward alternative routes of administration. One of the preferred methods is oral administration, as it can be easily supplied as a component of the fish feed (Mutoloki et al., 2015), having the potential to be adopted by aquaculture industries. There is so far no oral vaccine available for salmon lice, but the challenge is addressed in the research project Mucoprotect (NFR, 2021). Oral vaccines, however, need to confer immunity at clinically relevant levels while being affordable for usage in the pre-smolt stage. Fish immunology is a rising field of bewildering complexity just on the verge of inception. It will require years of research to achieve cost-efficient and sustainable vaccination against salmon lice.

### Repellents

Repellents

Another class of compounds, repellents, which are a subclass of semiochemicals, act on parasite olfactory systems, interfering with the settlement on the host. These chemicals act as masking compounds for salmon-derived kairomones, a sensory cue for salmon lice. Some natural compounds derived from plants have been tested as novel feed-through repellents and shown positive results by masking host-related compounds in Y-tube behavioral bioassays (O’Shea et al., 2017). Interestingly, even compounds derived from other fish have been shown to act as repellents, significantly reducing the infection rate of L. salmonis (Hastie et al., 2013). Despite showing promising results in laboratory conditions, these repellents require further validation of their efficacy and cost-efficiency in open farms. It will likely be
challenging to solve the problem of salmon lice infestation solely by introducing repellants due to the rapid dilution of chemical substances in open sea, but they may be employed in combination with other treatments.

**NON-MEDICAL METHODS**

There is a shift toward the use of non-medical solutions to control salmon lice infestation levels (Overton et al., 2019). This is, among others, as a result of the broad resistance developed against all available chemical agents (Aaen et al., 2015). Preventive measures such as cage depth manipulations, anti-lice functional feeds, lice skirts, and lice traps are part of salmon louse management plans. The use of direct physical and mechanical removal of lice and cleaner fish is growing. Furthermore, the relevance of environmental effects, such as temperature and local wind, and current trends in salmon louse management strategies with antagonistic selective effects that delay louse development should be considered when choosing different approaches (Jevne and Reitan, 2019; Coates et al., 2021). Current and novel innovations used to pursue non-medical alternatives are summarized in Table 3.

**Preventive Methods**

**Cage Depth Manipulations**

Salmon lice larvae have evolutionary preference for residing in the upper part of the water column, a strategy to increase the likelihood of finding potential hosts (Heuch et al., 1995). This phototrophic behavior has been explored in countermeasures taken to prevent lice contact with fish. **Lice skirts**, where tarpaulin is wrapped 5–10 m around the upper part of salmon pens, may act as a shield to prevent infective stages of lice from entering the pens from outside the surface waters (Frank et al., 2014). The skirt may decrease the infestation levels, but it may also cause a serious decrease in oxygen levels available for fish inside the skirt (Stien et al., 2012).

Similarly, with **deep lighting and submerged feeding**, fish change their swimming behavior during the feeding process and are attracted to larger depths assumed to have lower lice larval concentrations. The lice population present at any given time on salmon was found to be lower with deep lighting alone than with submerged feeding alone (Frenzl et al., 2014). During the day, however, natural light may have an impact on the efficacy of deep lighting due to the preference of salmon for natural light and their migration to the upper part of the water column (Frenzl et al., 2014). Furthermore, submerged lights can have a negative influence because certain wavebands of light tend to attract lice and may therefore raise infection pressure (Alsvik, 2019; Bjørnstad and Solstad, 2019; Borset, 2019; Vatn, 2019; Andersen, 2020; Nordtug et al., 2021).

**Snorkel cages** create a barrier between salmon and parasites, where a net roof at a depth of 10–20 m in the salmon pen, with a snorkel at the center, keeps salmon in deep water. The purpose of the snorkel is to provide a protection zone with low lice larval concentrations that allows the fish to reach the surface to take air into their swim bladders while reducing contact with the infective stages of lice (Stien et al., 2016). In one commercial study, the use of snorkel-based technologies was reported to result in a substantial reduction of salmon lice (Geitung et al., 2019). Finally, when different strategies are integrated, they are more successful than if used independently (Jackson et al., 2018).

**Anti-lice Functional Feeds**

The stimulus substances in functional feeds are composed of pathogen-associated molecular patterns (PAMPs) that are recognized by the immune system as foreign using pattern-recognition receptors, initiating signaling that leads to immune response (Mogensen, 2009). Immunostimulants, which are feed additives that protect against salmon lice and secondary infections, have been developed and widely used in aquaculture. Available functional feeds in the market include exogenous nucleotides and yeast components that have given 11–41% reduction in *L. salmonis* infestation levels (Yossa and Dumas, 2016). In addition, feeds containing plant-based glucosinolates have been reported to reduce lice counts up to 25% in fish compared to control diets without glucosinolates (Holm et al., 2016; Skugor et al., 2016). These feed additives have to be applied for a prolonged period (3–10 weeks) and apparently do not provide long-term protection. Therefore, these methods should be regarded as a temporary supplement with the potential to be efficient, especially when combined with other methods.

**Lice Traps**

Salmon louse has several sensory systems that are involved in host location during the infective stages. These systems can be used as bait to attract lice in underwater traps (Nordtug et al., 2021). One such sensory system has to do with vision, which guides parasites to either a flickering light that resembles fish swimming through sunrays or a continuous light source. It has a longer distance range than mechanosensory and olfactory systems and is likely to be shared across lice species (Fields et al., 2018; Bjørnstad and Solstad, 2019). Furthermore, lice are capable of changing hosts during their adult life stage, thus making it possible to capture them in traps when changing hosts (Ritchie, 1997). These factors have contributed to the development of light-emitting traps (LET) with a light source and an air lift system to capture parasites (Pahl et al., 1999). LET represent an attempt to reduce sea lice infestation and risks of potential infection with smaller ecological impact and at a reduced cost when compared to the chemical treatments (Flamarique et al., 2009; Burridge et al., 2010). It has been shown that alternating light attracts adult salmon lice, whereas the larvae are attracted to continuous light (Flamarique et al., 2000). Thus, future prototypes of LET should have several light sources in order to efficiently capture lice at different life stages, and possibly be combined with salmon-related olfactory cues to enhance efficiency. Current LET based on the light-emitting diode have been tested under laboratory conditions and found to catch 70% of larvae and 8% of female adults, suggesting that females are probably also attracted to continuous light, although at a lower efficiency (Flamarique et al., 2009). Another prototype, by the Chilean company Indeso

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1. [https://www.fishfarmingexpert.com/article/usinglights-to-lure-lice-to-their-deaths/](https://www.fishfarmingexpert.com/article/usinglights-to-lure-lice-to-their-deaths/)
### TABLE 3 | Overview of non-medical and biological control strategies for salmon lice management.

| Non-medical methods | Description | Principle | Issues | Sources |
|---------------------|-------------|-----------|--------|---------|
| **Preventive methods** | | | | |
| Lice Skirt | Salmon lice position themselves at topwater columns: Barrier and avoiding contact, cage depth manipulations | Tarpaulin sheets mounted around the top of the salmon pen | Oxygen level drop in pen, slowed flow of water | Skirt (Stien et al., 2012; Frank et al., 2014) Snorkel (Stien et al., 2016; Wright et al., 2018; Geitung et al., 2019) Deep light (Hevrøy et al., 2003; Frenzl et al., 2014; Nordtug et al., 2021) Submerged cages (Glaropoulos et al., 2019; Oppedal et al., 2020) |
| Snorkels | Snorkel at the top of the net roof to keep salmon deeper in the water column. | Same as lice skirt but to a lesser extent. Feeding problems | | |
| Deep lights/Submerged feeding | By placing lights or feeding systems deep within the pen | Natural light may have impact on efficacy in daytime. No proper control with submerged feeding alone could increase salmon lice pressure as they are attracted to lights | | |
| Submerged cages | Submerged cage to avoid surface salmon lice | Negative buoyancy effect | | |
| Anti-lice functional feed | Immune boost in fish and decrease in the ability of lice to attach to fish. | Use of glucosinolate in salmon, making heme unavailable for lice. 17–25% reduction in lice, more research required Short term protection | | Burrells et al., 2001; Refstie et al., 2010; Covello et al., 2012; Holm et al., 2016; Skugor et al., 2016; Vossa and Dumas, 2016 |
| Light traps | Salmon lice traps | Trap with light source (LED) and air lift system capturing parasites Need for the attractants; prototypes need improvements and testing in the field. | | Flamarique et al., 2009; Nordtug et al., 2021 http://idsol.cl/, https://www.bluelice.no/english/ |
| **Physical delousing** | | | | |
| Thermal treatments (20–34°C) | Vulnerability of the lice to sudden changes in temperature | The fish are briefly passed through warm water, killing salmon lice. | Fish welfare | Elliot, 1981; Elliott and Elliott, 1995; Gismervik et al., 2019; Overton et al., 2019; Moltumyr et al., 2021 |
| Freshwater treatment | Salmon louse freshwater sensitivity | The fish are briefly passed through fresh water, detaching the lice | Fish welfare, Freshwater resistance, Lice is initially affected, but recover Attached lice survive using ions from the host | Wright et al., 2016; Holan et al., 2017; Hjeltnes et al., 2019; Overton et al., 2019 |
| Flushers/ Hydrolicer | Physical removal | Salmon lice are flushed out with jets of water while salmon move through a system in a boat or barge. | Fish welfare, Loss of scale, gill bleeding, and wounds | Nilsen et al., 2010; Gismervik et al., 2017; Hjeltnes et al., 2019; Overton et al., 2019; Waide et al., 2021 |
| Laser treatment | Shooting with laser and killing | The system scans and shoots lice with a laser while laser beam is reflected from mirror-like fish skin. | Fish welfare, Insufficient laser pulse lethality rate. | Frenzl, 2017; Bui et al., 2020 |
| **Biological control** | | | | |
| Cleaner fish | Salmon louse predator | There are various types of fish that naturally feed on salmon lice | Cleaner fish welfare, ethical issues, sustainability costs | Bjordal, 1991; Skittesvik et al., 2014; Imsland et al., 2015, 2018; Halvorsen et al., 2017; Powell et al., 2018; Overton et al., 2020 |
| Biopesticides | Baculoviruses, fungi, parasites | Baculoviruses that are lethal to the hosts Almost all insect pests have at least one parasite that attacks them | No virus, fungi, parasite identified yet for salmon lice | Sparks et al., 2008; Sporleder and Lacey, 2013; Kamita et al., 2017; Williams et al., 2017 |
in the process of being patented. LET often require additional testing in the open sea, where they are exposed to sea currents which transport all stages of lice to downstream waters. The velocity of sea currents is typically higher than the swimming speed of lice, which may reduce the efficiency of LET. Lice traps have the potential to be an environmentally friendly form of lice management, but concrete research on their effectiveness and shortcomings in turbulent water and sea cages, and their effect on other phototactic organisms, is necessary.

Physical Methods
Thermal Treatments
Salmonids can tolerate a temperature of 20–34°C for a limited period of time (Elliott, 1981; Elliott and Elliott, 1995). In thermal treatments, the lice's susceptibility to abrupt increase in temperature is exploited for delousing. The salmon are crowded in grow-out cages and pumped into a thermal treatment system installed in a ship before being bathed in hot seawater for 30 s on board and allowed to return to sea cages (Noble et al., 2018). While thermal treatments are an effective approach for delousing, some reports have revealed that these treatments may cause tissue injury and severe welfare issues for the salmon (Gismervik et al., 2017, 2019). Other reports, however, conclude differently. Exposure of fish to a temperature of 34°C for 30 s in a recent study did not result in a significant increase in acute lesions apart from fin lesions (Moltumyr et al., 2021).

Flushers and Hydrolicer
Sea lice can be dislodged by water jets by passing salmon into a water jet system to flush out lice. Three companies currently use mechanical lice removal systems: Flatsetsund (FLS) Engineering AS, SkaMik AS, and the Hydrolicer®. The fish is injected into the flushing system for lice removal during treatment. FLS and SkaMik use similar systems, with the former using a flush/spray to remove lice and the latter including a brush system (Gismervik et al., 2017). Hydrolicer® pumps fish into a confined piping system and vacuums out lice using inverse water turbulence (Erikson et al., 2018; Overton et al., 2019). The flushers are attached to a boat or barge near the salmon pens. Fish are briefly pushed into the flusher where detached lice are removed, and the salmon thereafter are returned to the pen. Significant removal of mobile lice using these systems has been reported. There are no published studies on fish welfare and mortality, but losses of scale, gill bleeding, wounds and salmon mortality have been recorded (Gismervik et al., 2017; Holan et al., 2017; Hjeltnes et al., 2019; Westgård, 2020). A recent study has assessed the mortality of various delousing methods and concluded that thermal and mechanical delousing have the highest overall median mortality (Walde et al., 2021).

Freshwater Treatments
Salmon lice are more sensitive to freshwater (Wright et al., 2016) and this vulnerability is targeted in the delousing process of freshwater exposure. Freshwater treatment has historically been used to treat amoebic gill disease, but the use for salmon lice treatment is novel (Powell et al., 2015). Historically, it has been observed that wild salmon may migrate up the river to get rid of lice (Pontoppidan, 1755). A recent study of freshwater treatments in Central Norway showed a high reduction rate of salmon lice in all stages, as well as a very high reduction rate of Caligus elongatus (Gaaso, 2019). However, some reports have claimed that some attached lice can tolerate transfer into freshwater for 24 h. Transcriptome data shows upregulation of the proline synthesis pathway, which is used to offset cellular stress due to environmental effects (Liang et al., 2013; Borchel et al., 2021). Freshwater immobilizes the lice, but they might revive when they return to seawater (Andrews and Horsberg, 2020). To avoid the revival of lice in seawater, it may be necessary to filter the water before disposal. Adult stages of L. salmonis can live in low-salinity waters through a host–dependent interaction, where the lice absorb ions from the host to replace ions lost to the environment. This mechanism increases their tolerance to freshwater (Hahnenkamp and Fyhn, 1985; Johnson and Albright, 1991). The lice also detach as a result of the mechanical effects of crowding and handling before freshwater treatment, but most lice detach during the freshwater exposure (Gaaso, 2019). These detached lice are affected by freshwater exposure and die due to the changes in osmolarity compared to the few attached lice (Wright et al., 2016; Ljungfeldt et al., 2017). So far, freshwater treatment is considered one of the environmentally sustainable methods for delousing with less strain on fish welfare, but it is more time-consuming and expensive than thermal and mechanical methods. Some concerns have been expressed about the possibility that the lice may develop freshwater resistance.

Optical Delousing
Optical or laser delousing is achieved using a system composed of machine vision and targeted laser pulse removal. The laser pulses are directed to a single parasite detected by a submerged automated camera unit scanning the fish. The data generated by the computer vision is continuously transmitted to the database to further train the machine learning system. The laser pulses do not seem to damage the skin of salmon, and the system is able to recognize the fish's eyes and thereby prevent harm to them (Frenzl, 2017; Bui et al., 2020). Recent research suggests the lack of lethality of lasers rather than the lack of target detection requiring alternative delousing approaches (Bui et al., 2020). Optical delousing is a promising approach where physics meets informatics and pattern recognition in a multidisciplinary environment. New delousing methods currently under development are exploiting the possibilities of optical delousing. However, proper evaluation of the procedure and increasing the laser effectiveness are critical.

USE OF BIOLOGICAL CONTROLS
Cleaner Fish
Cleaner fish live in symbiosis with other fish species and feed on dead skin, ectoparasites and zooplanktons (Morado et al., 2019). Since the 1980s, cleaner fish have been used in preventative measures against lice (Bjordal, 1991; Torrissen et al., 2013). The use of cleaner fish as defense against salmon lice has increased steadily since 2008, with about 60 million cleaner fish
Biological control using cleaner fish has become a strong favorite among salmon producers, as new approaches that are less strenuous for salmon are deemed necessary (Barrett et al., 2020). Nowadays, cleaner fish, which include lumpfish (Cyclopterus lumpus), corkwing wrasse (Symphodus melops), ballan wrasse (Labrus bergylta), goldsinny wrasse (Ctenolabrus rupestris), and cuckoo wrasse (Labrus mixtus), are a prevalent alternative to current delousing control methods (Overton et al., 2020). This method is considered to be economical and less strenuous to salmon than physical and medical treatments, and the general public accepts the use of cleaner fish more readily than chemical treatments (Groner et al., 2013; Imsland et al., 2018; Powell et al., 2018; Overton et al., 2020).

Despite the wide acceptance and immense benefits, mixed results of the commercial success of the method have been reported. Easily accessible feed pellets, zooplankton abundance in the water, and prey located in biofouling may reduce the need for cleaner fish to feed on lice (Imsland et al., 2015). Concerns have also been raised about unsuitable environmental conditions that may reduce the efficacy and increase mortality among species of cleaner fish. Reports of diseases and high mortality of the cleaner fish deployed in salmon farms and ethical consideration of using vertebrates listed in animal welfare legislation are frequent (Nilsen and Colquhoun, 2014; Treasurer and Feledi, 2014). In addition, most wrasses are wild-caught, which can affect the abundance and population dynamics of the wild stocks negatively, and the sustainability of the use must be justified (Skiftesvik et al., 2014; Halvorsen et al., 2017). More focused, evidentiary use of cleaner fish could increase their effectiveness and help ease economic, environmental and ethical issues.

Biopesticides
Biopesticides are compounds used, instead of broad chemical pesticides, to manage agricultural pests through specific biological effects. They include biocontrol products like natural organisms or substances derived from natural products, such as genes or metabolites from animals, plants, bacteria, or certain minerals, that are used to manage pests (Sporleder and Lacey, 2013). Additionally, there are several reports of parasites that can manipulate and control arthropod behavior. The diversity of arthropod-manipulatory parasites varies from viruses to worms (Sporleder and Lacey, 2013). Viruses have been produced as biological insecticides for the control of pests in forests and agricultural crops. Baculoviruses are large, occlusive dsDNA viruses that infect arthropods (Anderson and May, 1980; Cory and Myers, 2003; Elderd et al., 2013). Many studies have shown substantial and important benefits for crop protection with both natural and genetically modified (GM) baculoviruses (Kamita et al., 2017). Further research on the use of salmon lice parasites, such as viruses or fungi, as a substitute for conventional chemical treatments opens the door to smart biological control of salmon lice in aquaculture.

ENABLING TECHNOLOGIES
The 20-first century is the era of biotechnology and information technology. Data availability and technological advancements have aided humanity in a variety of ways. We address some of the technologies that are or could be useful in counteracting salmon lice.
Machine Learning

Machine learning (ML) uses computer algorithms that are improved automatically by experience, which can create models based on sampled data to make predictions or decisions without being explicitly programmed to do so. Computer vision represents an ML environment where it is impossible for traditional algorithms to execute specific tasks (Szeliski, 2011). For many years, computer vision has been used to identify and measure planktonic individuals (Kocak et al., 1999; Zheng et al., 2017; Luo et al., 2018; Li et al., 2020), making the operation more powerful than manual detection. The effects of the use of machine vision can be as strong as those of human experts.

Computer vision is utilized in pattern recognition and followed by laser shooting during optical delousing. It could also be developed to monitor the infestation levels of lice. In addition, studies of the behavior of planktonic lice, such as their responses to light stimulus, are carried out (Kvæstad et al., 2020). Besides, ML has been applied in the identification of diseased fish suffering from secondary infections based on mass spectrometry data (López-Cortés et al., 2017) and in a random forest-based approach for genome-wide SNP analysis (Jacobs et al., 2018). In future, ML has the potential to enable smart and autonomous control and monitoring of salmon lice infestations.

Monitoring of Salmon Lice

Computer vision may also be applied to monitor salmon lice infestations in salmon farms. This may imply the development of a fully automatic sea lice counter for continuous counting and sorting of sea lice on farmed salmon without the need for handling. The method provides a more comprehensive, impartial, and precise assessment of the lice situation in a fish cage. Since there is a limit on the maximum mean numbers of average female salmon lice per fish (Heuch et al., 2005), it is beneficial to have a system that provides real-time data for decision-making in intervention selection. Ecotone AS have developed a system called SpectraLice for this purpose, which can distinguish various stages of salmon lice using their proprietary hyperspectral imaging technology to detect light through the entire electromagnetic spectrum (Spectralice, 2021). Recently, the Norwegian Food Safety Authority (NFSA) approved the use of another louse counting technology, this time from Aquabyte, adopting their robust camera setup and patented
optical architecture in 56 cages (Redaksjonen, 2021). NFSA have also given Stingray permission to use their image-based lice count system in 15 more cages (Dronen, 2021). One significant benefit of enabling technologies in lice monitoring is that they reduce costs in the long term and eliminate the need for fish handling and manual counting, which improves fish welfare.

Breeding and Use of Lice Resistant Fish
Selective breeding based on phenotypic values of a phenotype is typically used to generate genetic improvement of a quantitative trait in a population (Narain and Mishra, 1975). Using the same concept, salmon lice resistance can be improved by breeding new generations of farmed salmon using fish from families with low susceptibility to lice infestation. It has been verified that some select populations exhibit significantly reduced needs for chemical treatment to control lice outbreaks (Gharbi et al., 2015).

QTL (quantitative trait locus) analysis for the evaluation of gene variation in the breeding candidate for genomic selection has been used to select lines that are resistant or have better tolerance to salmon lice (Aquagen, 2017). This method has been successfully used in the selection of salmon with higher degree of resistance against Infectious Pancreatic Necrosis (IPN), with fewer outbreaks of IPN in the short term (Houston et al., 2008; Moen et al., 2009). A crucial step to counteract the lice problem can be achieved through a breeding process, but it will likely take several generations of salmon to see the effect. A more direct approach will be to find the genetic differences between the Atlantic and Pacific salmon, since the latter is less attractive as hosts for sea lice, and use this genetic information in breeding or genetic modification of the Atlantic salmon (Moore, 2020; Robinson, 2021). This methodology is currently being developed as part of the CrispResist project sponsored by the Norwegian Seafood Research Fund (FHF).

RNA Interference
Technological advances in molecular biology approaches to salmon lice are an integral aspect of the study of gene function and identifying breeding targets. The key to salmon louse management could be found in the study of genes, and technical advancement in this area is warranted. RNA interference (RNAi) is a form of gene knockdown that targets mRNA (not necessarily only mRNA). For many years, RNAi technology has been applied in aquaculture research, contributing to our understanding of functional genomics and aquatic biology (Abo-Al-Ela, 2021). A schematic diagram is shown comparing RNAi to genome editing (Figure 2). The method of post-transcriptional silencing of genes using RNAi has been developed for salmon lice (Campbell et al., 2009; Eichner et al., 2014) and several important genes have been functionally characterized. RNAi has facilitated in the study of the molecular biology of the louse, such as the function of specific genes in developmental processes.

RNA interference screens have aided the study of host–parasite interactions, host recognition (Komisarczuk et al., 2017; Núñez-Acuña et al., 2019), and physiology at various life stages of lice (Sandlund et al., 2016, 2018; Komisarczuk et al., 2018, 2020; Braden et al., 2020; Guragain et al., 2020). RNAi has also facilitated in the functional studies of key genes involved in lice reproduction (Dalvin et al., 2009; Tröne et al., 2014; Eichner et al., 2015a; Khan et al., 2017; Borchel and Nilsen, 2018; Borchel et al., 2019; Heggland et al., 2019a,b). In addition, the method is used to identify the potential vaccine targets in C. rogercresseyi (Carpio et al., 2011; Maldonado-Aguayo and Gallardo-Escárate, 2014). The genes and pathways in salmon louse studied using RNAi are summarized in Table 4, which offers a broad range of information on gene function and various phenotypes resulting from gene knockdown.

Genome Editing
Genome editing, which includes precise manipulation of DNA sequences to alter the cell fate and organism traits, offers the potential to broaden our understanding of genetics and biology (Doudna, 2020). An attractive genome editing tool used in multiple organisms and cells, including arthropods, is CRISPR/Cas9 (Clustered, Regularly Interspersed, Short Palindromic Repeats/Cas9), which was discovered as a bacterial adaptive immune system (Ran et al., 2013). CRISPR/Cas9 genome editing can be utilized to target specific sequences in a genome and to destroy a specific gene activity or to modify the activity of the encoded protein (Anzalone et al., 2020). Furthermore, advancements in the Cas12 and Cas13 systems may open up new avenues for genome editing and RNA editing, respectively (Yan et al., 2019). Genome editing has resulted in a revolution in functional studies of genes by providing a tool for down to single nucleotide editing. This is done without leaving any foreign DNA in the edited organism/individual. Genome editing is already used to improve plant and animal traits and has a big potential both for targeted improvements and identification of traditional breeding targets. An international project that has as its goal to identify genetic salmon lice resistance markers in the Pacific salmon and use this information to modify the Atlantic salmon using the CRISPR/Cas9 technology has already been initiated. In contrast to salmon, where gene editing technology is well established, the technological development of CRISPR/Cas9 in salmon lice is more challenging because of problems associated with targeting of germline cells, the method of delivery, and the absence of a visible marker for mutant screening. When developed, genome editing methods for salmon lice will open a completely new toolbox and avenue for studies of salmon lice and likely offer great potential for the development of principles of salmon lice control. The genome sequence of salmon lice was reported in 2012 and provides a fundamental aid in identifying the targets.

FUTURE PERSPECTIVES
Over the last decades, numerous preventive methods and treatments have been developed, and scientific studies undertaken, to combat salmon lice. As we have outlined here, none of these methods have been highly successful in counteracting salmon lice infestations. Most preventive methods have shown some efficiency, and others have yet
TABLE 4 | An overview of RNAi studies and their outcomes in Lepeophtheirus salmonis.

| Targets/Pathway                  | Genes                                                                 | Developmental Stage | Phenotype                                                                                                                                  | Sources                  |
|---------------------------------|----------------------------------------------------------------------|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Tyrosine metabolism             | LsPAH; phenylalanine hydroxylase                                     | Nauplius I          | Molting and swimming defect                                                                                                             | Guragain et al., 2020    |
| Myotropins                      | LsMS; myosuppressin                                                  | Adult               | Muscle content reduction, defect on molting, spermatophore deposition and feeding                                                          | Komisarczuk et al., 2020 |
| Chitin synthesis pathway        | LsGFAT; glutamine: fructose-6-phosphate aminotransferase             | Nauplius I          | LsCHS1 – Swimming defects LsCHS1 and 2 – Swimming defects LsGFAT – phenotypic irregularities LsCDA5956 – Swimming defects                | Braden et al., 2020      |
|                                 | LsLAP; UDP-N-acetylglucosamine pyrophosphorylase                     |                     |                                                                                                                                             |                          |
|                                 | LsAGM; N-acetylglucosamine phosphate mutase                         |                     |                                                                                                                                             |                          |
|                                 | LsCHS 1 and 2; chitin synthase 1 and 2                              |                     |                                                                                                                                             |                          |
|                                 | LsCDA 4557, 5169, and 5956; putative chitin deacetylases            |                     |                                                                                                                                             |                          |
| Key molecular contents in egg strings, Hemicentin family             | LsFCGS 1 – 6; female cement gland secreted 1 – 6                     | Preadult II female  | Deformed egg strings preventing reproduction                                                                                               | Borchel et al., 2019     |
|                                 | LsFCGMB1; female cement gland membrane bound 1                      |                     |                                                                                                                                             |                          |
|                                 | LsFCGPO 1 and 2; female cement gland peroxidase 1 and 2             |                     |                                                                                                                                             |                          |
| CD36-like protein (scavenger receptor class B (SCARB) family)        | LsHSCARB; heme scavenger receptor class B                            | Adult female        | Enlarged oocytes, shorter egg strings.                                                                                                     | Heggland et al., 2019a   |
| Ferritin                        | LsFer1; secretory ferritin heavy chain homolog                       | Adult female        | Impaired oocyte and egg string development, reduced egg hatching, no blood uptake.                                                        | Heggland et al., 2019b   |
|                                 | LsFer2; secretory ferritin light chain homolog                       |                     |                                                                                                                                             |                          |
| Spermatophore generation        | LsMLSWP 1 and 2; Mucin-like spermatophore wall protein 1 and 2      | Adult male          | Unorganized spermatophores, decreased reproduction                                                                                         | Borchel and Nilsen, 2018 |
| Mucin-like spermatophore wall proteins                                  | LsTSC1/LsTSC2; tuberous sclerosis tumor suppressor protein complex   | Adult female        | LsTOR, LsTSC1/LsTSC2 – reduced viable offspring LsRheb – hypotrophy, and necrosis in subepithelia, halted egg string production LsRheb, LsRaptor, LsTSC1/LsTSC2, LsTOR – abnormalities in the intestinal tissue | Sandlund et al., 2018    |
| TOR pathway                     | LsTSC1/LsTSC2; tuberous sclerosis tumor suppressor protein complex   |                     |                                                                                                                                             |                          |
|                                 | LsTOR; target of rapamycin                                          |                     |                                                                                                                                             |                          |
|                                 | LsRheb; Ras homolog enriched in brain                               |                     |                                                                                                                                             |                          |
|                                 | LsRaptor; Regulatory-associated protein of TOR                       |                     |                                                                                                                                             |                          |
|                                 | LsRictor; Rapamycin-insensitive companion of TOR                     |                     |                                                                                                                                             |                          |
| Lipophorin receptor             | LsLpR; lipophorin receptor                                           | Nauplius I, preadult II female, and adult female | Larvae – no phenotype Adult – female lice produced 72% less offsprings                                                                  | Khan et al., 2018        |
| Sodium–potassium pump           | LsNa+K+–ATPase; sodium–potassium-ATPase                             | Nauplius I, preadult II female | Larvae – defect in muscle development Adult – impairment in feeding and reproduction                                                      | Komisarczuk et al., 2018 |
| Fibronectin type II (FNII) domains expressed in tegumental type 1 glands | LsFNI1 1, 2, and 3; fibronectin type II 1, 2, and 3                 | Preadult II female and adult male | No visible phenotype                                                                   | Harasimczuk et al., 2018 |
| Heme peroxidase                 | LsHPX1; heme peroxidase 1                                            | Copepodid           | Decreased swimming activity, abnormal leg development                                                                                  | Øvergård et al., 2017    |
| Microsomal triglyceride transfer protein                                | LsMTP; microsomal triglyceride transfer protein                      | Preadult II female, young adult female | Offspring with reduced yolk content                                                    | Khan et al., 2017        |

(Continued)
to be tested commercially. We foresee that a key to future solutions could be unlocked through genetic studies of both sea lice and the Atlantic salmon, as well as of their physiological and ecological interactions. In addition, vaccine research, sophisticated engineering devices, and improvement in non-medical methods can provide us with the necessary tools to reduce the damage inflicted by salmon lice infestations. The ultimate biological goal in the quest to control salmon lice might be to breed super-resistant salmon, but there would likely still be a constant fight or arms race between lice and lice management strategies, comparable to the situation for terrestrial arthropods in agriculture. Cleaner fish provides good protection but have limitations of fish welfare and high cost. Another option might be to breed salmon that has been genetically modified to produce compounds that repel salmon lice without harming humans or fish. Natural enemies, such as biocontrol agents, could be another strategy for louse control that is less harmful to humans and the environment. The industry is using a wide range of counteracting measures to treat salmon lice in aquaculture. We have pointed to different strategies used, and the rapid development trend within the non-medical treatments.

We believe that a combination of multiple strategies is preferred to combat salmon lice until novel and better solutions become available in the future. The agriculture like approach, such as crop rotation or leaving fallow for greater protection, could be developed. Identifying key biological mechanisms in host–parasite interactions, metabolic profiling, and omics studies are critical. Methods such as RNAi and genome editing will play a central role in these types of investigations. The quest for better means of controlling salmon lice should not be stopped, and research activity should continue.

AUTHOR CONTRIBUTIONS

AMB and PG conceived and designed the study. PG, AMB and MT wrote the manuscript, with intellectual inputs from YO, PW, and ASB. All authors have reviewed and approved the manuscript.

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**TABLE 4** | Continued

| Targets/Pathway                  | Genes                                      | Developmental Stage | Phenotype                                                                 | Sources                                      |
|---------------------------------|--------------------------------------------|---------------------|---------------------------------------------------------------------------|----------------------------------------------|
| Ionotropic receptors            | LsalIR25a; ionotropic receptor 25a         | Nauplius I          | Knockdown larvae settled on non-host fish that were rejected by wild-type lice | Komisarczuk et al., 2017; Nuñez-Acuña et al., 2019 |
|                                 | LsalIR8b; ionotropic receptor 8b           |                     | Chemosensory system not fully activated                                   |                                              |
|                                 | LsalIR8a.1; ionotropic receptor 8a.1       |                     |                                                                           |                                              |
|                                 |                                            |                     |                                                                           |                                              |
| Ecdysone receptor               | LsEcR; Ecdysone receptor                   | Copepodoid Adult    | Intestinal and muscle tissue abnormalities. Hypotrophy in neurological tissue, gonads. Combination with LsRXR knockdown resulted in complete molting arrest | Sandlund et al., 2016                       |
|                                 |                                            |                     |                                                                           |                                              |
| Iron regulatory protein         | LsIRP1A; iron regulatory protein 1A        | Adult               | LsIRP1B – Shorter egg strings and fewer offspring                          | Tröste et al., 2015                         |
|                                 | LsIRP1B; iron regulatory protein 1B        |                     | LsIRP1A and 1B – increased expression of Ferritin                        |                                              |
| Chitinase                       | LsChi2; chitinase 2                        | Nauplius I          | Abnormal and decreased swimming activity, shorter cephalothorax, lower infection rate | Eichner et al., 2015b                      |
| RXR type of nuclear receptor    | LsRXR; retinoid X receptors                | Adult female        | Non-viable offspring                                                      | Eichner et al., 2015a                       |
| Secretory pathway               | LsKDELR; KDEL receptor                     | Preadult female     | LsCOPB2 – higher mortality and developmental defects                      | Tröste et al., 2014                         |
|                                 | LsCOPB2; COPI subunit1                    |                     | LsKDEL and LsCOPB2 – disturbed digestion and absence of egg strings       |                                              |
| Maternal yolk-associated protein| LsYAP; yolk-associated protein             | Adult female        | Lethality and deformity of offspring                                       | Dalvin et al., 2009                         |
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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