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REVIEW

REVIEWS IN Aquaculture

Antiparasitic approaches and strategies in European aquaculture, with emphasis on Mediterranean marine finfish farming: Present scenarios and future visions

George Rigos[1] | Francesc Padrós[2] | Eleni Golomazou[3] | Carlos Zarza[4]

[1]Institute of Marine Biology, Biotechnology and Aquaculture, Hellenic Centre for Marine Research, Attiki, Greece

[2]Facultat de Veterinària, Universitat Autònoma de Barcelona, Barcelona, Spain

[3]Department of Ichthyology and Aquatic Environment – Aquaculture Laboratory, School of Agricultural Sciences, University of Thessaly, Volos, Greece

[4]Skretting Aquaculture Innovation, Stavanger, Norway

Correspondence
George Rigos, Institute of Marine Biology, Biotechnology, and Aquaculture, Hellenic Centre for Marine Research, 46.7 Athinon – Souniou ave, 19013 Anavissos, Attiki, Greece.
Email: grigos@hcmr.gr

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Abstract

Parasitic infections can be occasionally severe in the European marine aquaculture industry, including the Mediterranean region, as they can incur considerable financial losses. Due to the lack of commercial vaccines, therapeutic approaches seem the only measure to battle parasitic outbreaks. Integrated strategies and increased resilience of the hosts, may limit to some degree the level of infestation. Ectoparasitic therapy is traditionally based on baths, with few exceptions. Several antiparasitic compounds have been registered in European aquatic medicine to combat mainly salmon sea lice; however, few of them are readily used against Mediterranean fish parasites. Formalin and less commonly hydrogen peroxide baths are applied against ectoparasites in the Mediterranean region. Most of the registered anti-lice antiparasitics have limited potential perhaps due to their adverse environmental impact. Future therapies against fish parasites will rely mainly on effective substances ensuring consumer, animal, and environmental welfare. Ideally, dietary antiparasitics such as praziquantel exhibiting mild environmental impact and high efficacy against a wide range of pathogens should be adopted. Moreover, combined strategies such as integrated pest management, involving various management practices with limited use of chemicals, should be a priority for specific parasitic outbreaks. The information presented in this review can guide future research and promote effective and prudent parasite control practices for Mediterranean-farmed fish.

KEYWORDS
antiparasitics, aquaculture, baths, dietary, efficacy, Mediterranean, parasites, therapy

1 | INTRODUCTION

Aquaculture is still the fastest-growing food production sector, providing more than half of all currently consumed seafood (214 million tonnes), while at the same time, world fisheries production has levelled off.[1] As in all animal production systems, diseases may seriously threaten the well-being of aquaculture enterprises. This challenge mainly depends on the range of pathogens that invaded both established and new farmed fish species.[2] The risk of diseases spreading from wild to farmed fish is also a considerable concern in aquatic medicine.[3] Climate change is not disputed and the triggering effects of global warming on disease pathogenesis should also not be neglected.[4]

Any attempt to thoroughly assess the economic impact of disease on finfish production is handicapped by incomplete information on

mortalities, reduced growth, therapeutic expenses, and other related costs. Parasites among other pathogens, can substantially affect aquaculture production and incur hatchery losses as high as 20%.[5] It has been estimated that the annual grow-out loss due to parasites is up to 10% of the harvest size, with an annual cost that approaches $10 billion in global terms.[6]

Parasitic diseases can be controlled using different approaches,[7] according to their particular characteristics and biological cycle. The use of antiparasitics may be the primary measure, although mechanical, biological, and immunoprophylactic approaches are also available, as more sustainable solutions.[8] Increasing the resilience of the hosts (broodstock selection, nutrition), represents also a powerful tool to battle fish parasites.[2] The management of parasitic infections in aquaculture is regardless of the applied measures, a constant challenge that is further complicated by the limited availability of licensed products, as well as concerns, related to environmental, host, and consumer welfare.[8]

Unfortunately, while for many of these antiparasitic substances, the relevant data from studies on humans or terrestrial farmed species is widely available, such information is generally narrowed for farmed fish. This limitation may challenge the effectiveness of dosing schedules against fish pathogens since in some cases, the required knowledge might be partially extrapolated.[9]

Despite the global diversity of aquaculture, European finfish production and specifically that developed in the Mediterranean region is largely concentrated on a few species. Gilthead seabream (*Sparus aurata*) and European seabass (*Dicentrarchus labrax*), are the main farmed species,[10] followed by meagre (*Argyrosomus regius*), Atlantic bluefin tuna (*Thunnus thynnus*), greater amberjack (*Seriola dumerilli*) and red seabream (*Pagrus major*), that are produced to a lesser extent. The production of the two dominant species alone (gilthead seabream, European seabass) approximates 464,000 tonnes, which accounts for almost 20% of the total value of the European aquaculture.[11] Greece is the top producer of marine finfish in the Mediterranean region (European part), accounting for 14% of the total production in weight (126,400 tonnes) and 16% in value (USD 561 million) in 2019. Other countries such as Spain, Italy, Croatia, Malta, and Cyprus are also considerable marine fish producers in the region.[11]

The acceleration of aquaculture production in the Mediterranean has been attributed to the use of floating cages, as the ideal shoreline in the region offers a wide choice of farming sites. Cage aquaculture has grown rapidly during the past decades, moving toward the development and use of more intensive cage-farming systems.[12] The intensive use of sea cages has allowed higher volumes of fish biomass but accidentally has contributed also to the dispersal of parasitic diseases.[13]

Within the framework of Mediterranean aquatic medicine,[14,15] the control of the important parasitic diseases with the use of therapeutic drugs has been relatively limited mainly due to legal restrictions on their particular use in fish farming. Knowledge about therapeutics, experience in tested substances for specific diseases and availability of commercial products is much less developed compared with other fish species. While the direct cost of other diseases was recently quantified in the Mediterranean region,[16] the economic loss due to parasitic diseases has not been possible for assessment yet.

The main aim of this review was to assess the current knowledge on the use of drugs to control parasitic diseases in European finfish farming, with particular interest in Mediterranean fish mariculture. Another objective was to offer a critical overview of the chemical substances used or that could potentially be applied, and related aspects such as delivery methods, efficacy, safety, environmental issues, legal concerns, and other technical aspects. The use of natural remedies to confront fish parasites has been reviewed elsewhere[17] and was not commented herein. Ideally, the outcome of this review will provide future perspectives for the use of chemical medicines for fish and perhaps integrated strategies to combat parasitic diseases efficiently while considering environmental and consumer safety.

2 | PARASITIC DISEASES IN MEDITERRANEAN FINFISH AQUACULTURE

As in other aquaculture regions, infectious diseases caused by parasites are a considerable problem in Mediterranean finfish farming. A detailed description of parasitic diseases has been recently discussed,[14,15,18] and specifically reviewed for European seabass,[19] sparids,[20,21] and meagre.[22]

Based on the pertinent literature and field knowledge, the main parasites of Mediterranean marine farmed fish are highlighted in Table 1. These mainly include ectoparasites such as the monogenean *Sparicotyle chrysophrii* in gilthead seabream, *Diplectanum aequans* in European seabass, and *Sciaenicotyle panceri* in meagre, copepods and isopods such as *L. kroyeri* and *Ceratothoa oestroides* in European seabass, and also endoparasites in the digestive system of sparids including *Enteromyxum leei* and *Enterospora nucleophila*. Moreover, other reviews have described relevant parasites in less commercialized species proposing as the most serious the digeneans *Didymosulcus katsuwonicola* and *Koellikerioides intestinalis* in Atlantic bluefin tuna and the monogenean *Zeuxapta seriolae* in greater amberjack.[36,55] Other important parasites such as the sanguinicolids *Cardicola* spp. and *Paradeontacylix* spp. seem to affect both established and novel fish species (gilthead seabream and greater amberjack).[51,54]

The development of parasitic diseases is strongly related to the parasite's life cycle, the rearing system, and the environmental conditions of the farming type. Infections caused by parasites with short life cycles such as ciliates and flagellate protozoans can be favoured in enclosed aquaculture systems,[56] with limited water exchange such as tanks operating in flow-through or RAS systems, or ponds and lagoons that facilitate the fast multiplication of several forms of the parasite cycle.[57,58] In contrast, fish reared in cages are particularly prone to parasitic diseases with a long-term cycle,[59] where one or several forms of the fish parasite cycle are permanently present or attached to the environment of the cages and their surroundings.[60,61] This is the case of diseases caused by mainly monogeneans, but also by copepods and isopods.[36,39] Other parasitic infections as those induced by enteric myxozoans, microsporidia, or apicomplexa,[62] can also be found in both farming systems (unpublished data).

TABLE 1 Main parasites affecting Mediterranean-farmed fish species.

Pathogen	Host	Target tissue	References
Ectoparasites			
Protozoa			
Amyloodinium ocellatum	Unspecific	Gills/skin	[23,24]
Cryptocaryon irritans	Unspecific	Gills/skin	[25,24]
Cryptobia sp.	ESB	Gills	[24,26]
Monogeneans			
Diplectanum spp.	ESB	Gills	[27–29]
Sparicotyle chrysophrii	GSB	Gills	[30,31]
Furnestinia echeneis	GSB	Gills	[32]
Zeuxapta seriolae	GA	Gills	[33,34]
Neobenedenia girellae	GA	Skin	[35]
Diplectanum sciaenae	ME	Gills	[22]
Sciaenacotyle panceri	ME	Gills	[22]
Isopods			
Ceratothoa oestroides	GSB, ESB	Oral cavity	[36,37]
Copepods			
Lernanthropus kroyeri	ESB, GSB	Gills	[38,39]
Caligus minimus	ESB	Gills	[40–42]
Endoparasites			
Microsporidia			
Enterospora nucleophila	GSB	Intestine	[43]
Myxosporeans			
Enteromyxum leei	GSB, RSB	Intestine	[44,45]
Sphaerospora dicentrarchi *S. testicularis*	ESB	Intestine, testes	[46,47]
Apicomplexa			
Cryptosporidium molnari	GSB, ESB	Stomach, intestine	[48]
Sanguinicolids			
Paradeontacylix spp.	GA	Gills and heart	[49–51]
Cardicola spp.	GSB	Gills and kidney	[52–54]

Abbreviations: ESB, European seabass; GA, Greater amberjack; GSB, Gilthead seabream; ME, Meagre; RSB, Red seabream.

3 | THERAPEUTIC CONTROL OF PARASITIC DISEASES: LEGISLATION, GENERAL CONSIDERATIONS PERTAINING TO TREATMENTS, AND PARTICULAR CONCERNS REGARDING THEIR USE IN FARMS

In Europe and particularly in the European Union (EU), most registered antiparasitics (https://www.ema.europa.eu/en/veterinary-regulatory/marketing-authorisation-veterinary-medicines) have been initially applied to combat sea lice infecting Atlantic salmon (*Salmo salar*), and eventually, few of these drugs were licensed in non-salmon producing countries, including some of the Mediterranean ones. However, in the Mediterranean scenarios, the target fish species are different; sea lice for example are not a problem but other copepods such as *Lernanthropus kroyeri* may cause severe problems in European seabass.[39] Consequently, antiparasitics could be legally commercialized in some EU countries but the target species (salmonids) are not farmed while relevant parasites are present. Thus, the product could be used only as an 'off-label' and always under the responsibility of the prescriber. The scarcity of specific on-label antiparasitic medicines has been alleviated by the 'cascade' mechanism established by the EU Directive 90/676/EEC (Council Directive of 13 December 1990 amending Directive 81/851/EEC; on the approximation of the laws of the Member States relating to veterinary medicinal products). This mechanism provides a prescribing cascade to support the use of medicines authorized for fish elsewhere or in terrestrial animals when no suitable compound has been licensed to treat diseases in fish farmed in the region. However, in most cases, this cascade system is still considered exceptional and is applied under the responsibility of the veterinarian prescriber.

Apart from therapeutic measures, parasitic infections may be managed using preventive and more complex zootechnical strategies.[2] In most cases, due to the lack of vaccination, the mitigation of outbreaks mainly depends on chemicals. In other cases, however, the possibility to control parasitic infections at the farm level is much more complicated due to the complexity of the parasite life cycles. This necessitates the implementation of integrated therapeutic approaches combined with zootechnical strategies and preventive management in the form of integrated pest management (IPM) programs.[63]

Antiparasitic treatments in Mediterranean farming, as in other aquaculture systems, are primarily applied in two different ways including bath and oral administration,[64] although in rare cases for individual specimens (broodstock, valuable aquarium fish, and research animals), delivery by injection can be considered. The selection of the treatment type differs along with the characteristics of the parasites and the related environment.[8] For ectoparasites, the preferred therapeutic strategies are apparently bath treatments. On the other hand, oral delivery is always considered for internal parasites.[2,64] In all therapeutic cases, the interactions between the drug molecules and the drug pharmacokinetics in the fish compartment are paramount to predict the effects of the molecules as therapeutics.[65]

The efficacy of the treatment is directly associated with the effect on the developmental parasitic stage and the type of therapeutic applied. The chemical characteristics of the product used, the dosing schedule, and the treatment duration are the classical main drivers considered in bath treatments. However, other relevant factors such as the saltwater solubility, stability, and reactivity of the selected compound are not always considered, and sometimes strong differences can be found under varied environmental conditions.[66] Frequently, the parasitic life cycles involve developmental free stages such as eggs, swimming, and larval stages,[67] which should be considered for therapeutic success.

From a general perspective in veterinary medicine, the two most relevant aspects concerning the decision-making process for therapy application and from the producer's point of view, are efficacy and animal safety, although environmental, consumer, and worker safety should be considered as well. Thus, in many cases, the choice of treatment strategy is not only dictated by the scale of the system to be treated and the efficacy of the therapy, but also by economics.[8] Infected fish are treated when a parasitic disease has spread to an extent that the health of the fish is immediately endangered, commonly expressed as increased parasitic load and/or fish losses.

A few important principles must be respected when designing therapeutic attempts against parasites. Fish therapeutics may be toxic to the fish above certain levels and should be seriously controlled, considering also that diseased fish are relatively weak and may be extremely sensitive to chemical exposure. Advisedly, the lower effective drug amount should be preferred, acknowledging that subcurative dosing may generate drug resistance.[68]

The safety of the therapy to treated fish is also an important aspect for the farmer since otherwise, the results of overdosing may be devastating for the wellbeing of the treated stock. Ideally, the decision to use a specific antiparasitic therapy should be made in conjunction with the environmental parameters, since water temperature usually increases the toxicity of fish medicines applied in water.[69] Antiparasitic baths are apparently riskier for treated fish since the quantities used are much higher compared with oral therapy. While any overdosed drug may be toxic at high water temperatures, the safety of the treated species emerges especially with bath-administered chemicals, because they are readily absorbed through the gills among other body barriers.[70] Improperly used bath medicines may induce different toxic side effects in treated fish. For example, some of the most pronounced hazards of applying a bath include gill and skin damage caused by formalin, neuro-toxicity caused by organo-phosphorus compounds and, oxidative stress caused by hydrogen peroxide.[70,71] On the other hand, the safety of drugs administered in feed is rarely a problem, due to a wide range between therapeutic and toxic doses.

To ensure the safety of consumer health, it is paramount to bear in mind that the farmed fish are intended for human consumption; thus, safety aspects related to the presence of residues should be considered. EU legislation has established guidelines for the proper use of medicines in animals including fish, to ensure consumer safety. The first step in the process of safety evaluation of veterinary products used in animal production is the determination of the Acceptable Daily Intake (ADI). This concept was first introduced in the 1960s by the Council of Europe and later updated by the joint Food and Agriculture Organization (FAO)/World Health Organization (WHO), a merging that produced the Expert Committee on Food Additives (JECFA). ADI is a parameter determined by the JECFA and reflects the chemical amount that can be ingested daily without side effects. Estimation of ADI is based on the no-observed-adverse-effect level (NOAEL), the amount of a substance that shows no toxic effects. Calculation of the maximum residue limit (MRL) for veterinary drugs is based on ADI and represents the maximum concentration of residue resulting from the use of a veterinary drug that is recommended to be legally permitted. The Committee for Medicinal Products for Veterinary Use (CVMP; https://www.ema.europa.eu/committees) of the European Medicines Agency (EMA; https://www.ema.europa.eu), is responsible for drafting opinions on the safety of veterinary medicines and the proposal of the MRL. Another parameter regulating the use of all antimicrobials is the withdrawal time (WT), which represents the time from the last treatment and the collection of the edible animal tissues. The estimation of WT is based on the drug's MRL, while in specific cases where no specific WT is defined or the use of the cascade is declared, a 500-degree day period is enforced (EU regulation No 37/2010; on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin).

4 | ANTIPARASITIC TREATMENTS IN MEDITERRANEAN AQUACULTURE: DELIVERY SYSTEMS

4.1 | Bath treatments

Bath treatments in Mediterranean farming are regularly used to control gill and skin ectoparasites (e.g., monogeneans, isopods, copepods)

TABLE 2 Hyposalinity schemes against various ectoparasites of Mediterranean-farmed fish.

Pathogen	Fish species	Hyposalinity scheme	Efficacy	References
Cryprocaryon spp.	Gilthead seabream	10‰, 3 h, four consecutive treatments, 3 days apart/8‰–10‰, 1–3 h	High	[58,75]
Euplotes sp.	European seabass	8‰–10‰, 1 h	High	(Rigos et al. unpublished results)
A. ocellatum	Gilthead seabream	0‰–2‰, 1 h	Low	

in caged fish. Application of baths in cages requires complex and weather-dependent logistics as well as the use of large amounts of therapeutic products, which makes them one of the most costly and time-consuming activities among cage health management activities. In rare cases, ciliates and flagellates can also be found in fish reared in cages,[72,73] but the most serious problems are observed in fish reared in tanks, raceways, or ponds, particularly in breeder tanks and nursery and on-growing facilities, and even research facilities using flow-through or recirculation systems.[74] In several cases, infections are associated with common ectoparasites of marine fish with direct cycle, mostly protozoans, or less frequently monogeneans.[2] In these instances, as water volumes of the rearing units are relatively small and the logistics of fish management are not as complicated as in cages, bath treatments are more suitable and easier to be applied. In some occasions, treatments can be performed in the rearing tank or fish can be collected and treated in a separate tank, container, or recipient.

4.1.1 | Hyposalinity

Freshwater or hyposalinity baths are considered therapeutic baths and are applied mainly at land-based facilities. However, due to their simplicity, freshwater is not considered a therapeutic molecule. Freshwater is used to debilitate or kill marine parasites by direct osmotic shock. Freshwater osmotic shock is particularly efficient for small ectoparasites attached to the skin, fins, or gills, not hiding under epithelial structures, such as flagellates (*Cryptobia* sp., *Ichthyobodo* sp.), *A. ocellatum* trophonts and *Cryptocaryon* sp.[58,75] These parasites are directly exposed to the freshwater bath; the osmotic shock effect is very fast as they are small-sized organisms and exposure time can be short. Recommended exposure doses for different Mediterranean species are set out in Table 2. The effect is lower in larger parasites such as monogeneans,[76] crustaceans, or isopods that can be more tolerant to osmotic shock. In contrast, marine fish, although also exposed to freshwater, can develop allostatic osmoregulatory mechanisms for a long time that can usually compensate for a certain time. Nevertheless, as opposed to euryhaline fish species, hyposalinity baths were not fully tolerated by pure marine fish.[75]

In some cases, mucus overproduction associated with the disease can modify the efficacy of the treatment and require longer bath exposure times to achieve the same results as under normal conditions. Freshwater used in the bath is usually available from the public water network or wells, although, in many areas in the Mediterranean, freshwater availability can be limited during some periods. Freshwater should be stored in water tanks or reservoirs when larger volumes are required. The physico-chemical and microbiological quality of freshwater should always be tested before the treatments to avoid any unexpected problems related to water quality. Seawater and freshwater temperature should also be taken into account to minimize problems associated with thermal shock.

4.1.2 | Formalin

Baths in a formalin solution are undoubtedly the most commonly used therapy against ectoparasitic infections in aquaculture,[77] and currently the most popular antiparasitic approach in Mediterranean aquaculture. Its effect on parasites is associated with high but unspecific chemical reactivity (mainly alkylation) of formaldehyde, the main component of formalin solutions. Formalin baths can be virtually used in all farming types and a variety of related aspects of its aquaculture use have been recently reviewed.[78]

In the context of fish medication, formalin is usually described as a 37%–40% formaldehyde solution dissolved in water. In Mediterranean aquaculture, it is used in hatcheries and nurseries to control problems associated mainly with the proliferation, of external protozoan ciliates and flagellates such as *A. ocellatum*[79] and *C. irritans*.[75] In those cases, its efficacy can be limited due to the presence of life cycle forms of parasites that are resistant or are not affected by the molecule. Formalin baths can also be used to control monogenean parasites and although they can be occasionally applied in tanks to control monogenean infections, in the Mediterranean represents the main treatment against *S. chrysophrii* infections in sea cages. The significant antiparasitic efficacy of formalin has been observed experimentally against *S. chrysophrii* in gilthead seabream,[80] *Microcotyle* sp. In red porgy (*Pagrus pagrus*)[81] and *D. aequans* in European seabass.[82] Formalin dosing schedules are shown in Table 3. These may vary, depending on the farming system, the targeted disease, fish status, and environmental conditions.

Possible side effects to fish from formalin baths necessitate careful preparation of the dosing schedule and titration. A typical mistake during baths deals with mixing up formalin and formaldehyde concentrations. Another consideration is the presence of dissolved organic matter, which can create faster decay of formalin. Readjustment of the dosing is advised in those cases. While water temperature is not considered an issue for formalin treatments in the normal ranges (17°C–25°C) of Mediterranean aquaculture, oxygen levels in the

TABLE 3 Formalin dosing schedules used against the ectoparasites of Mediterranean-farmed fish.

Pathogen	Conditions/species	Dosing schedule	References
C. irritans	Tanks, ponds/juveniles, broodstock of various species	100 ppm (1 h), 2 treatments 7 days apart/ 100 ppm (3–4 h), 4–5 consecutive days	[75,20]
A. ocellatum	Tanks/larvae of gilthead seabream	25–200 ppm	[79]
S. chrysophrii	Growers, juveniles of gilthead seabream	150–200 ppm (1 h)	[20]
D. aequans	European seabass	300 ppm (1 h)	[82]
	Earth ponds/adults of European seabass	375 ppm (1 h)	[83]
Microcotyle sp.	Cages/red porgy	150–200 ppm (1 h)	[81]

treated cage are crucial. The oxidation process of formalin to carbon dioxide and water naturally consumes oxygen, which may constitute a serious problem in the aquaculture systems.[78] Oxygen depletion during formalin treatments is commonly compensated by the addition of oxygen and its levels should be constantly monitored during baths.

Formalin can irritate fish[84] and provoke behavioural changes during treatments,[85] such as early excitement and increased swimming activity followed by lethargic behaviour, and thus fish should be monitored during therapy. Formalin treatments in cages as in all bath applications are difficult due to the complex logistics required concerning net management, tarpaulin placement and treatment preparation, delivery, and control of the operations. Compared with Atlantic salmon bath treatments for sea lice where in many cases, fish are transferred to bath barges,[8] these procedures are followed 'on-site' at Mediterranean fish farms using tarpaulins and tend to be much more difficult, complex, and risky because the large size of the cages used for grow-out. Tarpaulin treatments can be also performed using the so-called open skirt technique,[86] although the environmental risk of the process is considerable. More environmentally friendly closed tarpaulin bags have been made for sea lice treatments in salmon.[87]

Standard formalin baths in Mediterranean cages produced large amounts of formaldehyde which after treatment are released into the marine environment. The environmental fate of formaldehyde has not yet been fully assessed. The compound simply breaks down into carbon dioxide and water as oxidation occurs when comes into contact with the aquatic environment.[88] Moreover, it does not bioaccumulate because of its high water solubility, and it is readily biodegraded by bacteria and sunlight (biodegradation and indirect photodegradation). Notably, it has been estimated that under aerobic conditions in freshwater and water temperatures of around 20°C, formaldehyde is completely decomposed as early as 30 h.[89] The rate of disappearance of formaldehyde in seawater treated with formalin has been assessed and seemed also to be affected by aeration.[90] In particular, formaldehyde reached the detection limit concentration within 8–19 days, but its degradation was shorter when aeration was included (within 6–10 days). Consequently, although formaldehyde seems to degrade fully after a certain period in marine water, the potential adverse environmental effects of released formalin before its complete degradation remain unknown. The toxicity of formaldehyde has not been determined in non-target marine organisms.

Attention should be also given to the methanol concentrations (10%–15%) included in formalin solutions to prevent the formation of paraformaldehyde, which could be highly toxic to fish. It should be noted that methanol may act as an inhibitor of formaldehyde degradation in the aquatic environment.[91] Moreover, methanol persistence in the aquatic environment and its possible residues in treated fish deserve some attention, although its toxicity is much lower compared with that of formaldehyde (reviewed by Leal et al.[78]).

The wide use of formalin baths in aquaculture has also raised concerns relating to consumer's safety. Formaldehyde, the main component of a formalin solution, is actually a natural intermediate metabolic product of living organisms produced during amino acid metabolism, which at high exposure doses may cause acute toxicity.[92] However, formaldehyde is not clearly a bioaccumulative chemical, as indicated by the lack of the MRL requirement. Indeed, insignificant differences were found between formaldehyde concentrations in control tissues and tissues from cultured olive flounder (*Paralichthys olivaceus*) and black rockfish (*Sebastes schlegeli*), after exposure to formalin baths of 100–500 ppm for 1 h.[90]

Realistic measures to mitigate the release of high volumes of formalin after bath treatments in the environment should be prioritized in the future. For example, it could be feasible to a certain point, that treated water from the tarpaulins may be pumped into movable bags/tanks while at the same time, clean water is pumped into the treated cage with the bag. This handling could remove most of the treated water which may remain for a few days, until the decomposition of formaldehyde is completed, before being released back into the environment. The general concept of this strategy is one of the recent steps in Norwegian delousing therapy where well boats accommodate fish and treated water for managing parasitic infestations.[93] The use of well-boats for treating large numbers of pumped fish from cages on-board,[8] can solve some of these problems although such investment is extremely expensive and seems rather premature for Mediterranean aquaculture.

In conclusion, formalin baths are indeed very effective against a long list of ectoparasites affecting farmed finfish in the Mediterranean. However, research on its decomposition in the marine environment and potential toxicity effects, especially in the long term, is rather poor. Since that formaldehyde has been classified as a potential carcinogen by the International Agency for Research on Cancer (IARC), it is not unlikely that the compound will be banned for use as a fish antiparasitic and other more eco-friendly solutions will have to be found.

4.1.3 | Hydrogen peroxide

Hydrogen peroxide (H_2O_2) is a common bath-administered chemical used against fish ectoparasites, which is also used as a disinfectant in aquaculture and in numerous other non-medical and medical applications. H_2O_2 activity is related to its oxidative action[94] and breaks down into oxygen and water,[95] without any other by-products. Commercial formulations of concentrated H_2O_2 can normally be found in 35%–40% concentrations as disinfectants. Some formulations have been specifically produced as aquaculture disinfectants while others are specifically licensed as antiparasitic treatments for the salmon industry, but not specifically for Mediterranean species. The lack of residues in the treated animals and its natural degradation has made H_2O_2 particularly attractive for use in aquaculture, mainly from the point of view of the consumer and the environment. Hence, there is no established MRL for H_2O_2 for food-producing species.[96]

In contrast, the high oxidizing activity of the compound[94] may cause toxic effects to the treated fish such as irritation and chemical damage in the epithelia. H_2O_2 toxicity for fish has attracted much attention, and it varies considerably in different fish species, life stages, and water temperatures.[97] Baths with H_2O_2 may cause a potential risk to treated fish due to mucus damage in epithelial tissues[98] thus, opening portal entry to bacteria. Another issue arising during its use as an antiparasitic bath is its stability (H_2O_2 is a thermodynamically unstable molecule) and variable activity in water that depends mainly on water temperature, pH, the presence of organic matter, or other substances. The water temperature effect, in particular, is well-known in Atlantic salmon treatments with H_2O_2, where increased fish mortalities are observed above 14°C and thus, the use of H_2O_2 is restricted to lower water temperatures.[99] The problems associated with the potentially detrimental effects of this molecule at high water temperatures could be a serious handicap for its use in Mediterranean aquaculture as most of the production activities take place at temperatures above 15°C. However, H_2O_2 seems safe for European seabass growers subjected to 200 ppm for 1 h at a water temperature ranging from 19°C to 24°C (Rigos et al. unpublished). Interestingly, in the same fish species a 50 ppm bath for 1 h, but a higher water temperature (26.5°C–27.5°C), caused a quick physiological stress response which appears to require more than 24 h period for full recovery.[100]

The use of H_2O_2 baths against sea lice is widespread since the 90s in salmon cages.[101] Later, escalating doses of H_2O_2 were used to cope with the increased resistance of sea lice to this compound,[102] thus leading finally to reduced use. However, the compound is the main anti-lice chemotherapeutic used in Norway.[103] H_2O_2 baths are very effective against helminths of greater amberjack,[104] a finding observed repeatedly in unpublished field trials in the Mediterranean region. In European seabass and gilthead seabream, H_2O_2 has been tested for the treatment of *A. ocellatum* and *S. chrysophrii* infections. For *A. ocellatum* treatment, a 100–200 ppm bath for 2 weeks was effective in infected European seabass.[105] *S. chrysophrii* oncomiracidia are reported to be sensitive to direct exposure to 50–200 ppm of H_2O_2 for 30 min, but juvenile and adults are much more resistant and require a higher dose (200 ppm, 30 min).[80] In contrast, eggs are resistant to these doses and exposure times; therefore, for monogenean treatments in cages, it is very important to clean or change the nets before the treatment. Similar dosing schedules are proposed for in situ treatments,[20] but as previously indicated, field application of H_2O_2 baths in Mediterranean aquaculture is risky and the fish reactions are more unpredictable due to problems of stability and oxidative activity of H_2O_2 in Mediterranean summer temperatures.

Baths with H_2O_2 are not deprived of environmental concerns. H_2O_2 is an oxidizing agent producing free radicals, which can lead to oxidative damage to proteins and membrane lipids and DNA damage.[106] The half-life of H_2O_2 is rather long in seawater and can range from 7 days at 15°C to 28 days when environmental parameters vary.[107] Consequently, residues of H_2O_2 in the water column can be toxic for several non-target taxa including crustaceans harbouring the vicinity of salmon farms such as the European lobster (*Homarus gammarus*),[108] copepods (*Acartia hudsonica*),[109] polychaetes (*Capitella* sp. and *Ophryotrocha* spp.),[110] and algae (*Lithothamnion soriferum*).[101] The estimated lethal thresholds of H_2O_2 were in the range of mg/L for the organisms tested. The potential environmental side effects of H_2O_2 use in Mediterranean aquaculture have not yet been assessed.

4.1.4 | Azamethiphos

Azamethiphos (AZA) belongs to the organophosphates group, one of the first chemical groups introduced for salmon delousing therapy.[111] This organophosphorus insecticide acts by inhibiting cholinesterase activity, leading to overstimulation and then paralysis.[112] The application rate for AZA baths is 0.1–0.2 ppm for 30–60 min. Residue depletion of the drug is rapid in the edible tissues of salmon and no bioaccumulation occurs; thus, zero MRL has been established for AZA.[113] In several salmon-producing countries including Norway, Ireland, Scotland, and Chile, AZA was registered for use in aquaculture. For the de-lousing of Atlantic salmon in Norway, it was first used during the 90s and was re-introduced in the next decade. The peak year for treatments was 2014, while treatments drastically declined since 2017.[114] The effectiveness of AZA is time-dependent, as prolonged bath treatments are more effective, reducing the number of applications required and the risk of developing resistance.[115] Two repeated administrations are recommended, 10–20 days after the first administration and an additional after 14 days. However, as the health effects are related to the continuous administration of AZA, the intermediate alternative use of non-chemical anti-sea lice treatments is proposed, allowing the fish to recover from the previous pharmaceutical administration.[116]

AZA has an immediate delousing effect on all lice stages apart from the sessile larvae.[111,117] The toxicity of the drug to both lice and fish seems to increase with water temperature.[118] The proposed dosing schedule of AZA for salmon was also found safe for the European eel (*Anguilla anguilla*), European seabass, and rainbow trout (*Oncorhynchus mykiss*).[119] AZA was orally administered (2 mg/kg for 5 days) to control *D. aequans* in European seabass and it simply decreased the number of parasites.[120]

Although the toxicity of AZA was determined as less severe compared with other bath-delousing chemicals for particular marine fauna such as the European lobster,[121] generally its presence in the marine environment is considered a threat or even a lethal agent to non-target species including lobsters, crabs, shrimps and mysids (*H. americanus*, *Metacarcinus edwardsii*, *Crangon septemspinosa*, *Praunus flexuosus*, *Mysis stenolepsis*), which may scavenge on salmon farms.[122–124] Lethal thresholds for AZA were measured in the range of μg/L in most of the above organisms with the exception of crab, which seemed more sensitive to the exposure of AZA (effects in the range of ng/L).[124]

On invertebrates, sensitivity concerning both survival and reproductive capacity differs between species and developmental stages. The increased sensitivity or raised activity of the active compound is proportional to the temperature's increase. AZA is neurotoxic affecting the immune system and the transport of molecules to cells. Also, the behavioural response is related to exposure to the drug, decreasing feeding efficiency and causing a delay in reflexive escape from predators.[125]

As a bath-administered compound, the use of AZA for Mediterranean aquaculture has limited potential due to the known practical issues associated with bath applications and more importantly, to the adverse environmental impact in the studied environments.

4.1.5 | Cypermethrin and deltamethrin

Cypermethrin (CYP) and deltamethrin (DEL) belong to the pyrethroids group, a group of synthetic analogues of natural pyrethrins. Both compounds are used as insecticides in veterinary medicine against ectoparasites of livestock and in aquatic medicine to combat salmon sea lice.[99] They act by preventing the closure of voltage-gated sodium channels that results in abnormal hyperexcitability, spastic paralysis, and death of the parasites.[126] Their recommended bath dosing schedules for fish are 5 ppm for 60 min and 2 ppm for 30 min, for CYP and DEL, respectively. The MRL of CYP is 50 μg/kg and of DEL 10 μg/kg.[127,128]

The efficacy of pyrethroids against salmon sea lice seems to be correlated with water temperature[111,129] and has been successfully assessed.[115,130] However, more recently, lice resistance to these chemicals was demonstrated.[131] Notably, in Mediterranean aquaculture, DEL significantly reduced *C. oestroides* that affects the European seabass.[132] Similar findings have been demonstrated previously but with a dose-dependence profile.[133,134]

The use of pyrethroids in aquatic medicine has raised toxicity concerns in various treated farmed fish species,[135–138] as they lack enzymes for pyrethroid's hydrolysis.[139,140] Behavioural changes such as aggressive behaviour and swimming performance are mentioned. Significant damage to the gills and liver followed by haemorrhages of secondary gill lamellae and hepatic cell necrosis of hepatic cells are the main histological lesions.[141] Histological changes are strongly related to oxidative stress and induced genotoxicity as pyrethroids modify the expression and activity of antioxidant enzymes.[140] In Atlantic salmon, different side effects were observed due to DEL exposure, suggesting a temperature-dependent response.[142] In European seabass, no toxicity signs were apparent based however only on survival rates.[134]

The dispersion and toxicity of pyrethroids as regards non-target organisms have been stressed.[122,123] Strachan and Kennedy[143] assessed the environmental fate and associated risks of anti-lice chemotherapeutics including pyrethroids, for non-target marine organisms and concluded that DEL was the most toxic among the chemicals tested. Particularly, these drugs have the potential to reduce physiological and reproductive adaptive capacity in target and non-target organisms.[144] The lethal effects of DEL on Northern shrimp (*Pandalus borealis*),[145] copepods (*Acartia clausi*, *Pseudocalanus elongatus*, *Temora longicornis*, *Oithona similis*)[146] and amphipods (*Eohaustorius estuaries*)[123] were in the range of ng/L. As in the case of AZA, the use of pyrethroids cannot be proposed as bath-antiparasitics in Mediterranean aquaculture, regardless of the positive results associated with their preliminary use against European seabass ectoparasites.

4.1.6 | Hexaflumuron

Hexaflumuron (HEX) is an acyl urea chitin synthesis inhibitor. Chitin synthesis inhibitors are involved in the moulting process and the formation of chitin, resulting in death. They inhibit egg fertility and hatching, being effective against sea lice.[147,148] It is intended to control sea lice infestations in farmed Atlantic salmon, rainbow trout, and other fin fish. The substance is recommended for use in bath treatment, under a dosing regimen of 2 ppm for 60–120 min. HEX has been authorized in some EU countries for use in plant protection products but it is currently classified as 'Not approved'.[149] Nevertheless, HEX is registered in plant protection products outside the EU. The established MRL of the drug for fish is 500 μg/kg.[149]

HEX bath has been proven to be efficient against *L. salmonis* in Atlantic salmon moults and compared with other chitin synthesis inhibitors treatments, it is the most effective against larval moulting to copepods in a dose-dependent manner.[150] However, the effect of chitin synthesis inhibitors on non-target invertebrate species in the marine environment is of great concern as they can affect many molecular mechanisms related to oxidative and cellular stress.[151] Toxicity trials in non-target organisms are missing from the pertinent bibliography. Since HEX was recently introduced as a bath medicine for fish in the EU and several concerns have already been stressed about its long-term deposition time and toxicity effects, its future use in Europe and especially in the Mediterranean area, is rather unpromising and perhaps will be strictly considered if accompanied with controlled removal of the treated water.

4.2 | Oral treatments

Dietary antiparasitic therapy offers specific advantages over bath treatments in certain cases of aquaculture medicine.[8] As opposed to bath treatments, oral therapy in cages is simple, fast, low-cost, and weather-independent. Although dietary antiparasitics are mainly

TABLE 4 Registered oral antiparasitics in EU aquaculture.

Antiparasitic	Type/active	Action	Dosage	Target pathogens	Fish	MRL (μg/kg)	Examples of commercial premixes	Legislation
Emamectin benzoate	Macrocyclic lactone	Reduces cell excitability	50 μg/kg, 7 days	*Sea lice*	Mainly salmonids	100	Slice	[152]
Diflubenzuron	Acyl urea	Inhibits chitin synthesis	3–6 mg/kg, 14 days	*Sea lice*		10	Lepsidon, Releeze	[153]
Teflubenzuron			10 mg/kg, 7 days	*Sea lice*		500	Calicide, Ektobann	[154]
Lufenuron	Benzoyl phenylurea		10 mg/kg, 7 days			1350	Imvixa (Chile)	[155]
Praziquantel	Pyrazino-isoquinoline	Disrupts cell membrane	10 mg/kg, 1 dose 150 mg/kg, 3 days	*Eubothrium* sp. *monogenenea*	Salmonids, e.g., gilthead seabream	20		[156]

directed to endoparasites such as subepithelial and systemic ciliates, myxozoans, and microsporidians, when fighting ectoparasites; however, concerns about adequate drug concentration on target tissues may arise. Other issues connected with dietary therapy in fish health management are related to reduced palatability of the diet and delayed medicated feed preparation in feed mills. A more detailed comparison between bath and oral delivery is given in the concluding section.

Table 4 provides the list of registered oral antiparasitics in EU aquaculture. While there is a vast amount of literature for most of the listed compounds concerning efficacy and other aspects of salmon farming, such information is very limited for Mediterranean-farmed fish. Available information on in-feed treatments for parasite control there is fragmentary and based on a limited number of experiments. Most of them are based on small-scale or experimental work or belong to grey literature. There is a lack of large-scale field trials that are necessary for escalation to commercial application. Studies should be implemented under controlled conditions, with standardized challenge procedures, followed by field assessment. The evaluation of the efficacy of non-chemical commercial natural extracts to combat Mediterranean fish parasites was not included in the objectives of this study.

4.2.1 | Emamectin benzoate

Emamectin benzoate (EMB) is an emamectin salt that belongs to the avermectin family of compounds isolated from the microorganism *Streptomyces avermitilis*.[157] The compound is a close relative of ivermectin, an antiparasitic drug that is effective against nematode and arthropod parasites in both livestock and humans, and is also used experimentally in aquaculture medicine.[158] In general, avermectins modulate specific glutamate-gated anion channels in synapses and muscle cells, thereby increasing the influx of chloride ions.[159] EMB is one of the first effective oral fish antiparasitics, that has been extensively used for decades to combat parasitic copepods of farmed Atlantic salmon (*Salmo salar*) in Europe and elsewhere.[160] EMB is marketed in the EU (active 0.2%) for the treatment of *Lepeophtheirus salmonis* and *Caligus elongatus* with a recommended dosing of 50 μg/kg for 7 days. The drug has an established MRL of 100 μg/kg.[152]

The concentrations of EMB measured in skin and mucus were higher than those found in the blood of Atlantic salmon, thus supporting the fact that the drug is suitable against copepods invading the external tissues of farmed fish.[161] There is a large body of literature on the use of EMB against sea lice in the major salmon-producing countries including Norway,[162,163] Chile,[164] Scotland,[160,165,166] and Canada.[167–169] Although the efficacy of EMB against salmon sea lice was very promising with longer-term protection[165] during the first period of application, due to its extensive use, signs of resistance soon emerged.[160,164] Exposure of sea lice to subtherapeutic/sublethal drug concentrations after treatment has also been suspected of developing resistance.[169] Resistance to EMB has required regulation of use in the field and the implementation of a more sophisticated strategy to combat sea lice with EMB, as part of IPM programs.[170] These approaches seem to have stabilized the increase of sea lice resistance to EMB.[171]

Apart from the wide use of EMB in salmon farming, the compound has been evaluated against parasitic copepods and nematodes of other finfish species reared in freshwater or marine environments. For example, the drug appears to be effective against the copepod *Salmincola californiensis* in freshwater-reared rainbow trout[172] and *S. edwardsii* on brook trout (*Salvelinus fontinalis*).[173] Similar results have been reported for the coelomic nematode *Philometra rubra* in wild-hatched striped bass (*Morone saxatilis*)[174] and for controlling natural infestations of copepods in economically important farmed fish species of India.[175] The high antiparasitic value of EMB has also been demonstrated in marine finfish reared in either a cold environment with *C. curtus* infestations in Atlantic cod (*Gadus morhua*)[176] or in warmer water against *Caligus* spp.-infected hybrid grouper (*Mycteroperca tigris* × *Epinephelus lanceolatus*).[177]

In Mediterranean aquaculture, the use of EMB is relatively limited although the first results of the drug's efficacy are rather promising. Indeed, the control of the copepod *L. kroyeri* was successful in cultured European seabass, with administered EMB dosages of 10–100 μg/kg for 7 days.[178] There are no published records of EMB use against the isopod *Ceratohoa ostreoides*, a pathogen of several Mediterranean-farmed finfish species, although in field trials limited action was evidenced, perhaps due to the peculiar parasitic habitat on the host (buccal cavity). However, recent on-site attempts against *C. minimus* infections of European seabass were very effective (Dourala, personal communication).

Dietary antiparasitics administered to fish are regularly released into the environment via faeces, other metabolic products, and also through uneaten medicated food pellets. The main metabolites of EMB in tested fish are N-demethylated products (9%–14%), but other minor polar residues have also been found.[179] Bile is an important excretion route in fish medicated with EMB, as opposed to urine production.[161,179]

The environmental toxicity of EMB in the vicinity of salmon farms has been widely investigated; however, to date, no studies have assessed the potential side effects of EMB in the Mediterranean environment. Notably, residues of the compound have been found to be widespread in the vicinity of salmon farms.[180–182] The persistence of EMB in the marine sediments underneath and around salmon cages has been attributed to its long degradation half-life (EFSA, 2012)[183] and hydrophobic nature, resulting in a potentially high risk of exposure of benthic organisms. The chemical action is non-targeted; therefore, other species of the same sub-phylum as sea lice may be exposed to the same mode of action.[180] Several studies have evaluated the toxicity effects of EMB in marine organisms. For example, concentrations causing toxicity to several planktonic copepods were considerably higher (range of ng to μg/L depending on copepod stage and species) than Predicted Environmental Concentrations (PEC) in the vicinity of treated salmon farms and suggest that the use of EMB for lice control is unlikely to adversely affect planktonic copepods (*Acartia clausi*, *Pseudocalanus elongatus*, *Temora longicornis*, and *Oithona similis*).[184] Similarly, the toxicity of EMB on the polychaete worm *Arenicola marina*, the crustacean *Corophium volutator*, and the mollusc *Cerastoderma edule* was evident (range of μg/kg dry sediment with evidence for species-specific sensitivity), at levels above the Environmental Quality Standards.[185] It has also been demonstrated that EMB exposure concentrations at several folds higher (range of ng/kg wet sediment) than the maximum measurement of the drug recorded in the sediment of salmon farms are toxic to American lobster (*H. americanus*).[186] Elsewhere, EMB residues were detected widely distributed in the benthic environment of salmon farms, inducing a significant effect on benthic ecology.[180] Therefore, the potential environmental risk of EMB use in aquatic medicine highlights the need for regulated application especially in new farming habitats.

Overall, EMB can be considered an ideal and suitable compound to be used against the copepods of Mediterranean-farmed fish, due to its high distribution in parasitized fish tissues, such as skin and mucus.[161] Additional research efforts are required to determine the pharmacokinetics (PKs) of EMB in selected fish species farmed in the region. The efficacy of EMB should be further assessed by field trials targeting copepods and isopods that invade Mediterranean-farmed fish. The toxicity of the compound on non-targeted organisms in Mediterranean environments selected for cage fish farming should not be neglected in future studies.

4.2.2 | Diflubenzuron and teflubenzuron

Diflubenzuron (DFB) and teflubenzuron (TFB) are benzoylphenyl urea insecticides with a history of applications in agriculture. They have also been used as a dietary anti-lice product in European salmon farming from the late 1990s–2000s, and later in Chilean farms. They act by interfering with the synthesis of chitin and disrupting the moulting process of the targeted organisms.[187] In Norway, soon after their initial use, both compounds were replaced by EMB and pyrethroids, due to reduced sensitivity; however, they were reintroduced later to fight sea lice.[188] DFB and TFB have been marketed in Europe, with recommended dosages of 3–6 mg/kg for 14 days and 10 mg/kg for 7 days, respectively. The MRL of DFB was recently re-established as low as 10 μg/kg,[153] while TFB has remained at 500 μg/kg.[154]

The efficacy of TFB has been evaluated with some success against salmon sea lice[189–191]; however, no scientific reports on the anti-lice efficacy of DFB are available. In the Mediterranean, DFB was tested using the recommended treatment schedule in European seabass infected with *C. oestroides*.[134] The drug effectively cleared the pre-adult and adult stages of the isopod over the therapeutic period. On the other hand, TFB was found to be ineffective for the control of the isopod *L. kroyeri*[192] or the treatment of monogenean *Diplectanum aequans*[193] in European seabass.

Since flubenzurones have demonstrated poor absorption across the gastro-intestinal tract of salmon (SEPA, 1999),[194] and their metabolism is minimal in fish,[195] considerable amounts of the parent compounds are expected to be excreted in the vicinity of fish farms. It has been proposed that the main excretion pathway is the liver–intestine cycle.[196] As in all fish dietary drugs, environmental pollution is also attributed to uneaten medicated feed. Due to the hydrophobic nature of both DFB and TFB, prolonged persistence in sediments under salmon farms lasts several months,[195] since chemical and microbial degradation or outwashing are minor pathways for these drugs.[188] Their persistence in the sediments below salmon farms has been blamed to create an ecological risk for non-target species that undergo moulting,[151,197,198] although they are relatively non-toxic to fish and shellfish.[129] Particularly, European lobster (*H. gammarus*) fed two environmentally relevant TFB doses (corresponding to 5% and 20% of a standard salmon medication; 10 mg/kg day), exhibited affected molecular mechanisms.[151] The same animal polluted with TFB (1 ng/g lobster), showed significantly reduced physiological responses.[197] Concerns on the polychaete *Capitella* sp. and its environmental predators have been reported due to TFB contamination.[198] The risk of DFB use on shrimp populations has been also demonstrated by model predictions.[199]

No published records of DFB and TFB sea-lice resistance are available in the literature considering that benzoylureas seemed a class of registered drugs where lice resistance is not reported to be an issue.[200] The use of flubenzurones as fish antiparasitics in Mediterranean aquaculture has small potential perhaps due to the poor results obtained from preliminary attempts against the ectoparasites of European seabass, reduced absorption of DFB and TFB in salmon and adverse environmental footprinting in the vicinity of salmon cages.

4.2.3 | Lufenuron

Lufenuron (LUF) is another benzoylphenyl urea insecticide that was discovered in the 1980s and subsequently marketed in animal health

and agriculture.[201] As a benzoylurea pesticide, LUF binds to chitin synthase causing inhibition of chitin biosynthesis.[202] LUF was introduced in the last decade in aquaculture medicine as a more bioavailable anti-lice agent compared with DFB and TFB,[155] although its absorption properties have not been investigated yet in the target farmed fish species. It is intended for use in Salmonidae for the control of sea lice infestations as a premix formulation. The proposed treatment consists in feeding juvenile fish for 7 days before sea transfer at a dose of 10 mg/kg. Its MRL has been determined to be 1350 μg/kg.[155] However, LUF premix is awaiting marketing authorization for the EU[203] due to environmental concerns, although it has been registered in Chile for use in salmonids. The high efficacy of LUF against sea lice was recently evidenced and attributed to the rapid impact on moulting processes.[204] Interestingly, LUF administered at 10 mg/kg eradicated the isopod *Gnathia maxillaris* from aquarium fish.[205] There is no academic information on the toxicity of the compound on non-target organisms. LUF is a new in-feed antiparasitic agent in fish medicine and consequently, any attempt to evaluate its potential as a fish antimicrobial in Mediterranean aquaculture is relatively premature.

4.2.4 | Praziquantel

Praziquantel (PZQ) is a synthetic drug that was discovered in the 1970s[206] and has exhibited remarkable efficacy against a wide range of endo- and ectoparasites infecting humans.[207] Although the PZQ mechanism of action is not completely understood, its antiparasitic efficacy is rapid and dramatic. The compound disrupts the parasitic integument, inducing spastic muscular paralysis.[208] Paralysis is possibly accompanied by a rapid calcium influx into the parasite, as the calcium channels seem the drug target.[209] Apart from being a human antimicrobial, PZQ is also widely used in veterinary medicine,[210] and to a lesser extent in aquaculture.

Based on a recent opinion of the Committee for Veterinary Medicinal Products (CVMP), PZQ was included in the group of 'allowed substances' (Annex to Commission Regulation No 37/2010), with a proposed MRL of 20 μg/kg.[156] In Norway, has been used for several years under special permission as an oral treatment against tapeworms (*Eubothrium* sp.) in Salmonidae.[211] In Australia and several other Asian countries including Japan, Vietnam, Thailand, Malaysia, and the Philippines, PZQ is also registered as a fish antiparasitic.[212]

There is a vast amount of literature on the control of fish Platyhelminthes by PZQ administered either by bath of via feed (reviewed by Bader et al.[213]). The drug has been tested against numerous fish parasites by applying various treatment schedules via feed using doses ranging from 7.5 to 800 mg/kg/day. Dietary PZQ has shown remarkable efficacy as a fish anthelmintic in most cases.[213,214] The use of PZQ to combat helminths of Mediterranean-farmed fish is also very promising.[215] In particular, PZQ administered at 150 mg/kg for 3 days showed >80% reduction of *Z. seriolae* at summer temperatures. Similar efficacy results were obtained when the compound was administered under the same regimen against *S. chrysophrii* infecting gilthead seabream (Rigos et al., in preparation), while PZQ occasionally reduced *Cardicola* sp. infection in field.

Due to its bitter taste, dietary administration of PZQ has been associated with palatability problems,[216] which could inevitably cause a failure of therapeutic attempts. Reduced intake of PZQ-medicated diets necessitates the inclusion of masking agents[217] and specific feed management to enhance feed acceptance. Absorption of PZQ seems to be promising in gilthead seabream (Kogiannou et al., in preparation) and yellowtail amberjack (*S. lalandi*),[218] reaching values as high as 50%, which is higher than the value estimated for terrestrial animals (3%–32%),[219–222] perhaps due to considerable first-pass effect on absorbed PZQ on livestock.[206]

PZQ has been used widely to treat human diseases for several decades without being blamed for developing resistance. Moreover, no records on reduced PZQ efficacy, have been released from Japan or other Asian aquaculture users. However, it is widely accepted that as with the use of all antimicrobials, extended exposure to subcurative doses may favour the development of microbial resistance. Notably, low doses of PZQ (10 mg/kg) used against the tapeworm *Eubothrium* sp. affecting Norwegian Atlantic salmon, have been associated with signs of developed resistance.[223]

In general, the effective doses used to treat flatworm infections in fish are much lower than the levels that cause adverse effects, especially when dietary dosing is used.[214] Some neurotoxic properties have been attributed to PZQ to justify the adverse reactions of treated fish when administered by bath.[224]

Publications on the ecotoxicological impacts of PZQ are limited. While there might be some environmental concerns for PZQ bath treatments and the toxicity effects on non-target organisms (reviewed by Norbury et al.[214]), the potential side effects of dietary PZQ are virtually inexistent due to the significantly smaller quantities required. Nevertheless, there is a need for more extensive effort to ascertain the actual impact of PZQ on aquatic organisms, although recent toxicity tests on non-target Mediterranean organisms showed no or mild toxic effects.[225] There, no evidence for toxicity signs was seen in *Pseudomonas* sp. and *Daphnia magna*, exposed to concentrations as high as 1 mg/L, which are unlikely to be found in the vicinity of Mediterranean fish cages.

PZQ seems, undoubtedly, to be the most promising dietary fish antiparasitic for Mediterranean fish farming and could constitute an important component in current aquaculture systems in the region, by treating a range of important fish parasites including helminths in gilthead seabream and greater amberjack. Further work should ensure that PZQ will remain a viable treatment option in the future, alone or as part of IPM practices. Full registration of a PZQ premix at the EU level is advised as a paramount necessity for pharmaceutical companies.

5 | ENVIRONMENTAL CONCERNS

Aquaculture activities without proper control and surveillance may considerably impact the surrounding environment.[226] Among these

practices, the discharge of treatment products is one of the most hazardous to the environment. Thus, the potential environmental effects of the various chemicals used for disease treatment in Mediterranean-farmed fish should be minimized when possible. These effects may vary depending on different aspects such as the amount of substance, the release of the treated volume, and the type of the affected environment. Nevertheless, the environmental effects of any chemical depend largely on the specific chemical characteristics of the used substance that may affect solubility in water, biodegradation, and persistence in the environment.

For example, when H_2O_2 comes into contact with water, it simply breaks down into oxygen and water. While produces zero-impact metabolites at post-degradation, some consideration must be given, however, to its residues in the water column which can be toxic for some non-target organisms. Formaldehyde, on the other hand, has more complex interactions when formalin is used in the aquatic environment (reviewed by Leal et al.[78]) and may vary from dissolved oxygen depletion to biocidal effects. The compound is highly soluble in water and its bioaccumulation in aquatic organisms is not expected. Moreover, it is subjected to strong biodegradation activity in the aquatic system. This is also well demonstrated in RAS systems, where the compound is progressively degraded by the microbiota present in the system. During both biodegradation and oxidation, formaldehyde is converted into formic acid, which is also considered a natural and highly biodegradable compound with low potential for toxicity effects.[227] Thus, in water, formaldehyde seems to have a relatively low environmental impact, and the main concerns are related to the amount of the substance released into the environment and its possible side effects before its complete degradation.

Other registered bath-administered anti-lice compounds such as AZA and pyrethrins have, in principle, low potential use in Mediterranean aquatic therapy due to the release of large chemical volumes and their adverse environmental impact in other environments. The same applies to dietary pesticides blamed for environmental persistence such as DFB and TFB, regardless of the smaller quantities used in feed medication. Further consideration of EMB as a suitable oral compound in Mediterranean aquaculture, necessitates full exploration of its degradation profile and toxicity on fauna in the new environments. Dietary administration of PZQ on the other hand, seems safe for Mediterranean non-target organisms and its potential environmental persistence is negligible (reviewed by Norbury et al.[214]).

Comparably, oral medication administered to caged fish has obvious eco-advantages over standard baths; thus, the latter measures should be restricted to more controlled environments with smaller water volumes, such as those found in land-based rearing facilities. Assessment of the environmental impact must be a priority for treatment selection; thus, dietary chemicals should obviously be preferred over bath applications when possible, considering the quantities used. For instance, differences in the released volume between bath-administered and dietary chemicals are apparent, when dosing schedules are considered. A characteristic example is given in Table 5. A typical 2-month summer treatment schedule against a *S. chrysophii* outbreak in gilthead seabream, may easily result in the release of tonnes of formalin in the environment. On the other hand, some kilograms of dietary compound (PZQ) are only discharged when oral medication is applied. However, no oral compound can reach the high

TABLE 6 Comparison between bath and oral administration of medicines.

Method	Advantages	Disadvantages
Bath	High efficacy on ectoparasites Applicable in most farming systems	Heavy labour, high cost, complex logistics Dependency on weather Low toxicity margin Crowding, stressful process High environmental impact Low efficacy against endoparasites Inability to perform in very large cages Water solubility in some cases
Oral	Applicable to all farming systems High toxicity margin Rapid, relatively cheap, ease of application Weather independency Low chemical amount and environmental impact Efficacy against endoparasites Wide toxicity margin	Fish anorexia Palatability of medicated diets Delays in feed mill preparation and delivery Low efficacy against ectoparasites Feeding management Necessity of metaphylaxis

TABLE 5 Comparison of environmental pollution schemes against monogeneans in gilthead seabream; hypothetical therapy model (10,000 m^3 net volume/50,000 kg fish), during a 30-day period in summer.

Administration mode	Dosing schedule	Treated volume/ biomass	Efficacy	Issues	Predicted amount in the environment
Formalin bath	2 treatments (200 ppm/1 h)	8000 m^3	High (100%)	Weather dependent, very laborious	1.6 tonnes of formalin
Medicated feed (PZQ)	2 × 3 days treatment (150 mg PZQ/kg fish/day)	50 tons	High (<85%)	Fish anorexia, unpalatability of diet, feeding management	22.5 kg[a]

[a]Exactly 50% bioavailability of PZQ in gilthead seabream (Kogiannou et al. submitted).

TABLE 7 Registered bath antiparasitics in EU aquaculture.

Antiparasitic	Type/active	Action	Dosage	Target pathogens	Fish	MRL (μg/kg)	Examples of commercial premixes	Legislation
Formaldehyde	Methyl aldehyde	Alkylation	150–200 ppm, 1 h	Protozoa, monogeneans	All species	0	Aquacen	
Hydrogen peroxide		Destructs membrane lipids and DNA	75–100 ppm, <1 h	Monogeneans, sea lice	Salmonids, greater amberjack	0	Several	[96]
Azamethiphos	Organophosphorus	Inhibition of cholinesterase	0.1–0.2 ppm, 0.5–1 h	Sea lice	Mainly salmonids	0	Salmosan, Trident Vet	[113]
Cypermethrin	Pyrethroid	Interferes with nerve cells	5 ppm, 1 h			50	Excis, Betamax	[127]
Deltamethrin			2 ppm, 0.5 h			10	AlphaMax	[128]
Hexaflumuron	Acyl urea	Inhibits chitin synthesis	2 ppm, 0.5–1 h			500	Alpha Flux	[149]

efficacy of formalin treatment against *S. chrysophii* yet. Therefore, until an equally effective dietary substance is released, modified treatment strategies should be adopted; for instance, less frequent formalin treatments combined with dietary compounds or more preferably IPM strategies with minimum use of chemicals.

6 | RECOMMENDATIONS ON TREATMENT STRATEGIES TARGETING IMPORTANT PARASITIC INFECTIONS OF MEDITERRANEAN-FARMED FISH

The treatment of parasitic infestations in Mediterranean farms is admittedly a challenge due to the complexity of the different aspects to be covered. To tackle these aspects, full knowledge of each parasitic cycle, transmission pattern, and epizootiology[228] in the different geographical scenarios of the Mediterranean region are essential for the efficient selection and design of the treatment schedule.[8] Antiparasitic treatments should be applied as soon as the problem is detected or the number of parasites exceeds certain thresholds. Attention should be paid to parasitic infections with treatment-resistant forms in their cycles (e.g., cysts, eggs) or with the presence of intermediate hosts within the facilities, as the reappearance of the problem is most likely. Special care should also be taken in developing resistance to certain antiparasitic substances, mainly after recurrent use in treatments. Combinations of different therapeutic strategies (oral and bath) are sometimes possible, allowing a certain synergic effect. A comparison between bath and oral administration of medicines is provided in Table 6. Oral treatments require less labour, are relatively cheaper and the logistics are much simpler than for bath treatments. Dietary medications also have wider safety margins and do not require potentially stressful management like baths. Moreover, all infected cages, ponds, or tanks can be treated simultaneously.

However, dietary therapy is not deprived of limitations and practical disadvantages. Serious restrictions on the legal use of antiparasitic molecules and the critical availability of specific commercial products for fish are serious concerns for certain Mediterranean countries. In addition, problems related to the manufacturing of medicated feeds at small (farm-level) or large scale (feed companies), and palatability of the medicated feeds, appetite, and feeding rates, which are similar to those described recently for antibacterials.[65] For certain diseases affecting particularly the digestive system (e.g., *Enteromyxum* and *Enterospora* spp.), although the active compound can easily reach the main affected tissues, the alteration of the intestinal mucosa may also alter the absorption and distribution of the medicine.

Variations between farms in the application and delivery of an oral treatment among individual fish, cages, sites, and seasons, may result in the exposure of fish and parasites to excessive or subtherapeutic doses,[229] being economically wasteful, increasing the risk of development drug resistance and environmental impacts.[230] For these reasons, oral treatments in Mediterranean aquaculture tend to be much more efficient when the levels of the parasite in the

TABLE 8 Proposed integrated treatment strategies against important parasitic diseases of Mediterranean-farmed fish.

Pathogen	Host	Antiparasitic	Dosing schedule	Other management practices
Protozoa	Various species	Formalin Hyposalinity	100 ppm (1–2 h) 8‰–10‰ (1–3 h)	In cage infections, need for deeper cage sites to break the parasitic cycle Renewal of the tanks/transfer of fish Attention to pure marine spp. tolerance Repeated baths may be necessary
Monogeneans	Gilthead seabream, European seabass Gilthead seabream	Formalin PZQ	150–300 ppm (1 h) 150 mg/kg (3 days)	Broodstock selection/genetic resistance Improved net/cage hygiene/faster replacement of nets, ROVs Coordinated treatments (whole site and/or area), following strategies Prevent contact with wild fish hosts Repeated baths/oral medication may be needed Enhance palatability of medicated diets with attractants Nutritional management (excess of iron)
Monogeneans	Greater amberjack	H_2O_2 PZQ	75 ppm (30–60 min) 150 mg/kg (3 days)	Improved net/cage hygiene Repeated baths/oral medication may be needed
Sea lice	Gilthead seabream, European seabass	EMB H_2O_2	50–100 μg/kg (7 days) 100–200 ppm (h)	Broodstock selection/genetic resistance Manual removal during grading or vaccination (*C. ostreoides*) Prevent contact with wild aggregated fish
Myxosporeans	Gilthead and red seabream	Functional diets (Sanacore)	0.2%–0.3% diet (30–60 days)	Nutritional management/reduced dietary fat Improved net/cage hygiene
Digeneans	Gilthead seabream, greater amberjack	PZQ	150 mg/kg (3 days)	Enhanced net/cage hygiene with regular removal of biofouling

facility are low or at early stages of the disease, rather than in advanced stages with a high prevalence of the disease and increased parasitic load.

The two main bath treatments used in Mediterranean aquaculture, formalin and H_2O_2, can be effective against ectoparasites in Mediterranean-farmed fish but not in all cases. Particularly in cages, the use of formalin baths requires complex logistics and careful calculation and assessment of the doses before and during the treatment which may have relevant environmental and labour risks. Application of formalin is also not allowed in certain countries and its future use is nowadays under discussion. Other substances (Table 7) can also be used as bath treatments, but their use also depends on national regulations and environmental concerns.

Antiparasitic treatments, while effective in the short term, should not be relied upon as the sole solution in Mediterranean finfish farms, as continuous treatment is not ideal. Instead, a multifocal approach is necessary for efficient parasite control, particularly in cage aquaculture where complete eradication is not feasible. To maximize parasite control and mitigate parasitic diseases, a multidisciplinary and integrated approach, including coordinated treatment strategies like IPM,[63] along with prophylactic measures such as broodstock selection, nutritional manipulation[231] and genetic disease resistance traits,[232] is highly recommended. Integrated parasitic treatment strategies, detailed in Table 8, encompass not only chemical use but also environmental control and management practices. For example, for monogenean and particularly *Sparicotyle* infections, the control of the environmental stages, particularly the attachment of eggs to substrates[233] is paramount and requires additional measures such as periodical net cleaning or net substitution and reducing net biofouling. Nutraceutical supply with dietary iron addition[234] is also advisable and even genetic selection strategies[235] and prevention of pathogen transmission between farmed and wild fish,[236] have recently been suggested to reduce the impact of sparicotylosis. Formalin and H_2O_2 appear to have limited efficacy against copepods and isopods affecting Mediterranean species so in this case, alternative bath treatments (Table 7) or supporting oral treatments have been suggested (Table 4). For the particular case of *C. oestroides*, manual removal during grading or vaccination has been an efficient management process, while in the case of European seabass infected by *L. kroyeri*, genetic improvement for disease resistance traits has shown promise,[237] in addition to dietary EMB which seems an effective anti-lice therapy. Additional control strategies used in other farmed species, like light traps and chemotropic disruption equipment could target sea lice in cage culture,[238] while skirts or surface nets may prevent contact between swimming stages and farmed fish.[86] Nutritional management, including the use of functional diets[239] and fat content reduction,[240] can be effective against enteric parasites like *E. leei* in gilthead seabream, and regular removal of dead fish and organic waste is advised to improve infection control in all rearing systems.[241] The management of *E. nucleophila* infection is currently limited due to its recent description and the microscopic nature of its spores, but water disinfection measures and removal of dead fish can help maintain sanitation in controlled environments.[242]

7 | FUTURE OF THE CHEMICAL ANTIPARASITIC THERAPY IN MEDITERRANEAN FINFISH AQUACULTURE

The impact of parasitic infections on Mediterranean-farmed fish populations will be undoubtedly a continuously increasingly challenging task. The biological aspects of the target parasites, the particular characteristics of the rearing systems, and the problems associated with treatment logistics render the control of certain parasitic diseases a rather complicated process. Further, the undisputed climate change-related enhanced pathogenicity and spread of fish parasites should be added to this challenge.

While the limited availability of licensed antiparasitic treatments remains one of the key barriers to effective parasite control in aquaculture, maintaining a high level of efficacy of the licensed antiparasitics and simultaneously holding antimicrobial resistance at minimum levels, seems a crucial priority. Proper disease management should involve accuracy in drug dose and delivery, minimum number of treatments, and chemical switching whenever possible. Other tools to confront fish parasites, such as nutritional manipulation and selective breeding for disease resistance, have the potential to aid the established therapeutic practices and thus, considerably reduce the number of treatments. Vaccination should be further progressed toward relevant parasites using modern technology,[243] while autogenous vaccines that are already adopted in Mediterranean aquatic medicine,[244] belong to the main future disease tools.

Discarded residues of commercial antiparasitics can be harmful to the environment by causing toxicity to non-target organisms and posing a risk for the development of resistance. The possible presence of chemical residues in edible fish tissues deserves equal concern. Reduction of chemical use, resulting from the involvement of new integrative antiparasitic strategies, will advocate for both the welfare of the consumer and the environment.

The development of new eco-friendly substances to treat fish parasites represents one of the major drivers of future innovation in aquatic medicine. The need for novel antiparasitics, therefore, mandates the identification of alternative effective treatments, since the development of microbial resistance necessitates new resistance-breaking solutions. The ultimate goal of screening for novel antimicrobials is the identification of promising candidates for further optimization and escalation toward commercial scale. In animal health, two identification strategies in drug discovery include phenotypic or target-based screening.[245] Focused efforts of drug development in aquaculture should be perhaps devoted toward those strategies. Although rather premature for aquatic medicine, artificial intelligence, a recent yet revolutionary approach in human medicine,[246] has a great chance to accelerate the discovery of efficient antimicrobial alternatives with lower chances of resistance generation.

In conclusion, the available antiparasitics will be always judged as a significant tool to reduce the impact of parasitic diseases in Mediterranean-farmed fish. However, they cannot be considered as the sole solution for parasitic diseases given to concerns related to the applicability, legal aspects, consumer health, and environmental impact. Conversely, ideal antiparasitic attempts should additionally employ multidisciplinary approaches such as IPM practices. Finally, future management strategies against parasites in Mediterranean aquatic medicine have to cope with the great challenge of the coming decades for intensive animal production; producing high-quality food in an ethical, consumer-targeted, environmentally friendly, and economically viable manner.

AUTHOR CONTRIBUTIONS

George Rigos: Writing – review and editing; software. **Francesc Padrós:** Writing – review and editing; methodology. **Eleni Golomazou:** Data curation; writing – review and editing. **Carlos Zarza:** Writing – review and editing; methodology; data curation.

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ORCID

George Rigos https://orcid.org/0000-0002-3148-6213
Francesc Padrós https://orcid.org/0000-0002-8610-5692

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