International Journal for Parasitology: Drugs and Drug Resistance 18 (2022) 87–102

Contents lists available at ScienceDirect

International Journal for Parasitology: Drugs and Drug Resistance

journal homepage: www.elsevier.com/locate/ijpddr

Praziquantel use in aquaculture – Current status and emerging issues

Luke J. Norbury [a], Sho Shirakashi [b], Cecilia Power [a], Barbara F. Nowak [a,c], Nathan J. Bott [a,*]

[a] School of Science, STEM College, RMIT University, Bundoora, 3083, Victoria, Australia
[b] Aquaculture Research Institute, Kindai University, Wakayama, 649-2211, Japan
[c] Institute for Marine and Antarctic Studies, University of Tasmania, Launceston, 7250, Tasmania, Australia

ARTICLE INFO

Keywords:
Praziquantel
Aquaculture
Parasite

ABSTRACT

Parasitic diseases are major constraints in fish mariculture. The anthelmintic praziquantel (PZQ) can effectively treat a range of flatworm parasites in a variety of fish species and has potential for broader application than its current use in the global aquaculture industry. In this review we report on PZQ's current use in the aquaculture industry and discuss its efficacy against various flatworm parasites of fish. Routes of PZQ administration are evaluated, along with issues related to palatability, pharmacokinetics and toxicity in fish, while PZQ's effects on non-target species, environmental impacts, and the development of drug-resistance are discussed.

1. Introduction

Praziquantel (PZQ) is a broad-spectrum pyrazino-isoquinoline anthelmintic that is effective against all forms of schistosomiasis in humans (Andrews et al., 1983). However, while highly effective at killing adult schistosomes, immature schistosomes show reduced sensitivity to PZQ (Xiao et al., 1985) and the treatment does not prevent reinfection (Chandiwana et al., 1991; Webster et al., 2013). PZQ has broad application and since it became available has been integral to control approaches at both the individual and community level against numerous platyhelminth infections (Wegner, 1984; WHO et al., 2009; Chai, 2013); in many cases being relied upon almost exclusively, for example in the treatment of many foodborne trematode infections (reviewed by Keiser and Utzinger, 2004). Along with an integral role in treating human flatworm infections, it is used extensively in veterinary practice (Andrews et al., 1983; Dayan, 2003; Doenhoff et al., 2009; Scala et al., 2016). However, PZQ is not effective against all platyhelminths, for example it is ineffective in treating *Fasciola* infections (Patrick and Isaac-Renton, 1992; Chai, 2013).

PZQ's effects on parasites can be dramatic and almost instantaneous; however, PZQ's mechanism of action is not completely understood. It has been proposed that PZQ binds to voltage-gated calcium channels altering membrane permeability to calcium, causing an influx of calcium and disrupting calcium homeostasis. In recent years there has been interest in transient receptor potential (TRP) channels as PZQ targets (Bais and Greenberg, 2018) and a schistosome TRP ($Sm.TRPM_{PZQ}$) activated by PZQ and with properties consistent with known PZQ effects on schistosomes has been identified (Park et al., 2019, 2021; Park and Marchant, 2020). Other proposed mechanisms of action include interference with adenosine uptake, or the possibility of multiple targets (current knowledge on mode-of-action is reviewed in Thomas and Timson, 2018, 2020). The broad-spectrum anthelmintic activity of PZQ appears to be based on several effects, which are dependent on the type of parasite, its location in the host, and the host's immune system, with more than one effect possibly in action against any one parasite population (Harnett, 1988).

PZQ has a wide margin of safety, and is generally considered safe in animals, with very low toxicity, and no genotoxic risks identified in yeast, bacterial, drosophila, and mammalian studies (Bartsch et al., 1978; Frohberg, 1984; Kramers et al., 1991). PZQ is widely used as a safe and effective dip or bath treatment for the removal of a range of parasitic flatworms from ornamental fish, elasmobranchs (sharks, rays), teleosts and turtles in residential aquaria, zoos, marinas and research laboratories (Moser et al., 1986; Thoney and Hargis, 1991; Adnyana et al., 1997; Stetter et al., 1999; Chisholm and Whittington, 2002; Vaughan and Chisholm, 2010; Hadfield and Clayton, 2011; Smith et al., 2017). Along with widespread use in human medicine, veterinary practice, and aquaria, PZQ has application in aquaculture. Here, we review PZQ use in aquaculture, including the advantages and potential issues associated with its applications for different parasites and hosts and in different farming environments.

* Corresponding author.
E-mail address: nathan.bott@rmit.edu.au (N.J. Bott).

https://doi.org/10.1016/j.ijpddr.2022.02.001
Received 24 August 2021; Received in revised form 13 February 2022; Accepted 17 February 2022
Available online 22 February 2022

2. Current use of PZQ in aquaculture

Worldwide food fish consumption continues to increase, with aquaculture predicted to account for 54% of total fish production and 60% of fish for human consumption by 2030 (Kobayashi et al., 2015; FAO, 2020). However, diseases are one of the main constraints on aquaculture, with a range of pathogenic organisms, including parasites, able to detrimentally impact fish health (Lafferty et al., 2015). Fish are common definitive and intermediate hosts for a variety of platyhelminth parasites (for reviews of fish parasites see Woo and Buchmann, 2012 and Ogawa, 2015) and several factors in aquaculture systems can exacerbate the consequences of parasite infections that would otherwise have minimal impacts on the health of wild fish populations (Lafferty et al., 2015).

PZQ has been an obvious control measure for platyhelminth parasites in the aquaculture industry. However, PZQ for the treatment of fish for human consumption is only registered for use in a number of jurisdictions worldwide, for only certain parasites under specific conditions. In Japan, PZQ is the active ingredient of Hadaclean (Bayer Ltd.), Benesaru (ASKA Animal Health Co., Ltd.), and Praziguard flavour for fish (Riken Vets Pharma Inc.), and there are clear guidelines on how it can be used. In 2000 the first of these products was approved by the Japanese government for the treatment of skin fluke *Benedenia seriolae* in perciform fish by oral administration and to treat sea-caged Japanese amberjack *Seriola quinqueradiata*; however, fish farmers have tended to prefer hydrogen peroxide bath treatment over PZQ because of its palatability problem. Since 2015, these products have been approved for use in Japan to treat the blood fluke *Cardicola opisthorchis* infecting cultured Pacific bluefin tuna *Thunnus orientalis* and are commonly used by tuna farmers as the only available treatment measure. Several other Asian countries including Vietnam, Thailand, Malaysia, and the Philippines allow PZQ use in fish for food consumption (ASEAN, 2013).

Another example of PZQ use in aquaculture occurs in Norway, where it is used as an oral treatment for tapeworms in Salmonidae, such as rainbow trout *Oncorhynchus mykiss* and Atlantic salmon *Salmo salar* (Lunestad et al., 2015). However, PZQ is not listed for use in fish for human consumption by all governments and its use in aquaculture is typically 'off-label' under special veterinary justification. For example, in Australia at the time of writing there are currently four valid permits granted by the Australian Pesticides and Veterinary Medicines Authority (APVMA) that allow use of PZQ in aquaculture—for the treatment of blood flukes in Southern bluefin tuna *Thunnus maccoyii* and other Thunninae, and for the treatment of *B. seriolae* and gill fluke *Zeuxapta seriolae* in yellowtail kingfish *Seriola lalandi* (APVMA, 2018, 2020a, 2020b, 2020c).

Within this restricted regulatory environment, PZQ is used in the treatment of various fish parasites and is an essential anthelmintic with a distinct and valuable role to play in aquaculture (Ogawa, 2015; Bader et al., 2019). However, the efficacy of PZQ treatment varies depending on a range of factors, including the parasite, host, delivery route (including palatability in oral delivery), and environmental conditions, and evaluation of efficacy should be performed in the host-parasite target system (Bader et al., 2019). Additionally, maximum residue limits, withdrawal periods, and safety in the target fish species needs to be considered when making evidence-based treatment decisions.

3. Delivery

When deciding on the most appropriate mode of PZQ delivery, parasite, host, and environment need to be considered. The scale of treatment should be considered—many studies are undertaken in experimental settings, and certain methods are more practical, due to convenience and cost, when treating larger fish populations as encountered in industry.

3.1. Oral delivery and palatability issues

Oral administration, with PZQ mixed in feed can be the most convenient and cost-effective form of delivery, especially when treating large populations of fish or in net pen culture. It is commonly used in aquaculture, including for the treatment of *Cardicola* spp. infections of *Thunnus* spp. in Japan and Australia (Ishimaru et al., 2013; Power et al., 2019; APVMA, 2018, 2020c).

A major drawback of oral delivery is that it relies on the fish still eating despite the infection and that uniform delivery can be hard to achieve, leading to inadequate and/or inconsistent dosing among the population. Parasitised animals may have decreased appetites (Sitjà-Bobadilla et al., 2006), feeding hierarchies may exist (McCarthy et al., 1992), or the feed may be unappealing (Yamamoto et al., 2011). PZQ has a bitter taste, with low palatability, and there have been several reports of problems pertaining to feed rejection, vomiting and reduced feed intake in several fish species (Sitjà-Bobadilla et al., 2006; Williams et al., 2007; Yamamoto et al., 2011; Forwood et al., 2013a, 2016b; Partridge et al., 2014). This can be a significant issue, Yamamoto et al. (2011) reported up to a 95% reduction in feed intake in chub mackerel *Scomber japonicus* when PZQ was added to feed pellets at a PZQ dose of 150 mg/kg (dietary inclusion level of 0.5%; S.Shirakashi unpublished), and low palatability of medicated feed has resulted in variations in efficacy and occasions where high treatment doses are ineffective at removing parasites from various fish species (Hirazawa et al., 2004; Sitjà-Bobadilla et al., 2006; Williams et al., 2007, 2009).

The issue of palatability is linked to dietary inclusion levels; palatability issues can become more of a problem when PZQ is at higher concentrations. Lower concentrations of PZQ in feed have been tried; however, using lower concentrations is not always possible (Partridge et al., 2014). Similarly, no palatability issues were noted for Pacific bluefin tuna when 15 mg/kg BW PZQ was coated on semi-defrosted sand lance (Shirakashi et al., 2012a). Dietary inclusion level of PZQ was approximately 0.05% (S. Shirakashi, unpublished). When the dose required to effectively treat a parasite is relatively low, relatively low dietary inclusion levels can be used to deliver an effective dose, bypassing any palatability issues. However, when a higher effective dose is required (e.g. the treatment of *B. seriolae* in *Seriola* spp.; Table 3) it becomes more difficult to lower the dietary inclusion level and still deliver an effective dose.

Several methods to increase feeding rates have been reported. Lowering the PZQ dose (allowing for lower dietary inclusion levels) and extending feed times has been trialled with some success in *Seriola* spp. and spotted halibut *Verasper variegatus* (Hirazawa et al., 2004; Williams et al., 2007; Partridge et al., 2014), as has withholding feed for a period before treatment (Pool et al., 1984; Forwood et al., 2016b); however, denying food is less than ideal when trying to achieve maximum growth of fish (Yamamoto et al., 2011).

PZQ form and dietary application method can affect palatability (Partridge et al., 2014). As a result, different methods of including PZQ in feed have been trialled. These include using moist pellets, various methods of incorporating PZQ into feed pellets (mixing with powder, soaking, microencapsulation, use of nanoparticles), coating feed with stimulants or scents (commercial attractants, fish oil, krill extracts, sugar, or fresh garlic), or using coating or binding agents (carboxymethyl cellulose sodium salt, agar, gelatine) (Williams et al., 2007; Yamamoto et al., 2011; Blumenthal, 2014; Partridge et al., 2014, 2019; Forwood et al., 2016b; Pilmer, 2016). These techniques have had limited success. Delivery of only the (*R*) enantiomer failed to significantly increase palatability of PZQ (Partridge et al., 2017). Recently in Japan, a flavoured PZQ drug for aquaculture, Praziguard flavour for fish (Riken Vets Pharma Inc.) which claims to increase the palatability by 40 times, has been commercialized, but the detail of the product is unknown (Patent application 2020–179,894).

Several feeding techniques have been reported to overcome the palatability problem in some fish species. Mixing PZQ with carbon

powder and delivering in pellet form has been developed and used for treating skin flukes in *Seriola* spp. (Goto, 2019). When treating chub mackerel at PZQ dose of 150 mg/kg BW, which is equivalent to dietary inclusion of approximately 0.5% (S. Shirakashi unpublished), the palatability issue was overcome to a degree by administering PZQ with semi-defrosted frozen krill, after fish rejected PZQ-coated commercial pellets (Yamamoto et al., 2011). Similarly, no palatability issues were noted for Pacific bluefin tuna when 15 mg/kg BW PZQ was coated on semi-defrosted sand lance (Shirakashi et al., 2012a). Dietary inclusion level of PZQ was approximately 0.05% (S. Shirakashi, unpublished). Alternatively, to treat blood flukes in ranched Southern bluefin tuna in Australia, freshly caught sardines are injected with PZQ and then fed to fish, giving good results (Benetti et al., 2016; APVMA, 2020a). However, the lower effective PZQ dose required for the treatment of blood fluke infection and option to use a lower dietary inclusion level means palatability is less of an issue in tuna aquaculture.

Intubation, or oral gavage, can be used to deliver consistent amounts of PZQ to fish and has been successfully applied in certain situations (Pool et al., 1984; Kim et al., 1998; Williams et al., 2007; Forwood et al., 2016b). However, it is only a research tool; it is time-consuming, labour intensive and handling can stress fish, so is not a practical delivery method on a commercial scale.

3.2. Injection

PZQ injection into treated fish is the most direct method of delivery and ensures the correct dose. However, like delivery by intubation, it is labour intensive and stressful to fish, which explains why little research has been undertaken examining this form of PZQ administration. Its use is most practical when small numbers of easy-to-handle fish are to be treated, indicating possible utility for treating valuable broodstock, but not for wider commercial application. To date it has been utilised in experimental settings to successfully treat tissue-dwelling digeneans, *Posthodiplostomum minimum* and *Clinostomum. marginatum* metacercaria in bluegills and catfish, respectively (Lorio, 1989; Bader et al., 2018). However, intramuscular injection of PZQ at 20 mg/kg body weight (BW) was ineffective in treating *Nanophyetus salmincola* metacercaria in salmon (Foreyt and Gorham, 1988). Oral administration was ineffective against this parasite, and treatment failure may reflect the refractory nature of the metacercaria stage to PZQ treatment rather than a lack of drug absorption following injection administration (Foreyt and Gorham, 1988).

3.3. Bath and dip treatments

Bath or dip treatments allow for the uniform treatment of fish. Dips are generally undertaken at high concentrations for short durations, while baths are generally undertaken at lower concentrations and typically last from a few hours to several days. PZQ has low solubility in water and it is often dissolved in an organic solvent such as polyethylene glycol, ethanol, DMSO, isopropyl alcohol or glycerol prior to subsequent dilution and use (Schmahl and Taraschewski, 1987; Mitchell, 1995; Sharp et al., 2004; Buchmann et al., 2011). PZQ bath and dip treatments have been used to successfully treat a range of platyhelminth parasites, with effective doses starting from as low as 0.25 mg/L and duration typically ranging from 4 min to 2 days (Székely and Molnár, 1991; Mitchell, 1995; Kim and Cho, 2000; Sharp et al., 2004; Hoai and Van, 2014). See Tables 1–3 for specific treatment details. Bath treatments at 2.5 mg/L for 30–60 min to remove skin and gill flukes from *S. lalandi* provide an example of their use in a commercial setting (APVMA, 2020b). However, some bath treatments can require large amounts of PZQ for the required effect, and may be prohibitively expensive or impractical when needing to treat large volumes, for example in sea-cage operations. Additionally, bath treatments in sea-cages can be logistically difficult, and can be labour-intensive, weather dependent and stressful on fish. Furthermore, the release of large volumes of water containing PZQ can have negative environmental impacts and implications for resistance development (Crane et al., 2008).

Bath treatments of ectoparasitic monogeneans allows for treatment of the parasites even if they detach from the host, an advantage over oral administration. Bath treatments can be effective against endoparasites (see Tables 1–3). However, bath treatments may not be as effective when hypersecretion of mucus occurs (Forwood et al., 2013b; Reed et al., 2019), such as in response to gill monogenean infections (Thoney and Hargis, 1991; Noga, 2010).

Stocking density is extremely important when administering bath treatments, with instances of decreased PZQ efficacy against flatworms reported at higher stocking densities (Mitchell, 2004; Mitchell and Darwish, 2009). Treatment duration is important, and extending the duration of bath treatments allows for significantly lower PZQ concentrations to be used, while retaining or improving treatment efficacy. (Schmahl and Taraschewski, 1987; Székely and Molnár, 1991; Mitchell, 1995, 2004; Mitchell and Darwish, 2009). For example, Mitchell and Darwish (2009) showed that doubling the bath duration time for grass carp from 12 h to 24 h but dropping the PZQ concentration 12 × (9 mg/L to 0.75 mg/L) resulted in significantly better treatment efficacy against the Asian tapeworm *Bothriocephalus acheilognathi*.

4. Efficacy

Platyhelminths are traditionally divided into four groups—turbellarians, cestodes, digeneans and monogeneans—and except for turbellarians are entirely parasitic, with fish or other aquatic animals as hosts (Ruppert et al., 1994). Each group has distinct features, such as their respective life cycles, the fish species they infect, and their morphologies, which can influence the impacts they have on aquaculture and the efficacy of PZQ treatments (Bader et al., 2019). As such, while reviewing the situations where PZQ has been shown to be effective against platyhelminths in fish and its use in the aquaculture industry, the next sections will be discussed through the prism of these parasitic subgroupings.

4.1. Cestodes

Cestodes, known as tapeworms, are endoparasites. Due to their complex life cycle, cestodes are not common parasites in most aquaculture systems. The adult parasite typically resides in the digestive tract, and adult cestode infections in fish are usually asymptomatic, although several species can cause weight loss or morbidity if severe infections occur. Metacestodes (larval stage of cestode) present in fish muscle reduce the quality and market value of the fish; additionally, some species can cause zoonosis, for example, *Diphyllobothrium* sp. (Levsen et al., 2008; Lima dos Santos and Howgate, 2011).

Evaluating the effectiveness of PZQ in the treatment of cestodes in fish has focused on treating the adult stage of *B. acheilognathi* (see Table 1). Bath treatments with PZQ have been shown to be effective against *B. acheilognathi* in grass carp *Ctenopharyngodon idella*, as well as red shiners *Cyprinella lutrensis* and bonytail *Gila elegans* (Mitchell, 2004; Ward, 2007; Kline et al., 2009; Mitchell and Darwish, 2009; Iles et al., 2012). Doses as low as 0.25 mg/L for 24 h can completely eradicate the parasite from grass carp (Mitchell, 2004). Oral administration of PZQ through feed (105 mg/kg BW over 3 days) or intubation (35 mg/kg BW) is effective at removing this parasite (Pool et al., 1984).

Several other adult cestodes have been cleared from fish using PZQ as bath or oral treatments, including *Senga* sp., *Atractolytocestus huronensis*, *Khawia sinensis* and *Bothriocephalus scorpii* (Sanmartín Durán et al., 1989; Lewbart and Gratzek, 1990; El-Banna et al., 2008; Sudová et al., 2010). Taken together, these results indicate PZQ is highly efficacious against adult cestodes. However, there is uncertainty regarding the efficacy of PZQ against other cestode life stages. A 10-day bath of PZQ did not kill procercoids of *Nybelinia* sp. in the marine copepod *Tigriopus californicus* (Moser et al., 1986). Additionally, eggs of

Table 1
Use of PZQ in aquaculture against cestodes. B – bath, O – oral, I - intubation, Inj - injection. EXP – experiment, COM – commercial.

Parasite	Fish species	Delivery	Dose (mg kg^{-1} for oral, injection or intubation; mg L^{-1} for bath)	Efficacy dpt – days post treatment	EXP or COM	Reference
Atractolytocestus huronensis	*Oreochromis niloticus*	O; in feed (in ration) for 1 d	40 60	100% prevalence reduced to 10%	EXP: 50 L tank	El-Banna et al. (2008)
Atractolytocestus huronensis	*Cyprinus carpio*	O; I (in heat-treated amyloid vehicle), single dose	50	100% 4 dpt	EXP: 250 L tank	Sudová et al. (2010)
Bothriocephalus acheilognathi	*Ctenopharyngodon idella*	O: I (saline solution), single dose	35	100%, 7 dpt	EXP: 50 L tank	Pool et al. (1984)
		O; in feed (coated pellet), 2 min feed every 30 min for 3 d	105 over 3 d	100%, 6 dpt	EXP: 1600 L tank	
Bothriocephalus acheilognathi	*Ctenopharyngodon idella*	B, 24 h. Fish stocking density at 6 g/L.	0.25	100%, 0 dpt	EXP: 10 L tank	Mitchell (2004)
		B, 12 h. Fish stocking density at 69 g/L.	2.8	100%, 4 dpt		
		B, 24 h. Fish stocking density at 69 g/L.	0.7	100%, 4 dpt		
Bothriocephalus acheilognathi	*Gila elegans*	B, 24 h	1.5	100%, 1 dpt	EXP: 454 L tank	Ward (2007)
Bothriocephalus acheilognathi	*Ctenopharyngodon idella*	B, 6 h. Fish stocking density at 60 g/L	12	Prevalence reduced to 10%, 3 dpt	EXP: 22 L tank	Mitchell and Darwish (2009)
		B, 12 h. Fish stocking density at 60 g/L	9	66.7% prevalence reduction, 3 dpt		
		B, 2 × 12 h, 3 d apart. Fish stocking density at 60 g/L	1.5	96.7% prevalence reduction, 3 dpt		
		B, 24 h. Fish stocking density at 60 g/L	0.75	100%, 3 dpt		
		B, 24 h. Fish stocking density at 120 g/L	0.75	Prevalence reduced to 15%, 3 dpt		
Bothriocephalus acheilognathi	*Cyprinella lutrensis*	B, 24 h	6	100%	EXP: 1892 L pool	Kline et al. (2009)
Bothriocephalus acheilognathi	*Cyprinella lutrensis*	B, 2 × , 19 d apart	2.5	100%, 2.5 mpt	EXP: 1098 L mesocosm	Iles et al. (2012)
Bothriocephalus scorpii	*Scophthalmus maximus*	O; I, 3 doses over 3 d	5/d	100%, 12 dpt	EXP: 1200 L seawater tank	Sanmartín Durán et al. (1989)
Khawia sinensis	*Cyprinus carpio*	O; I (in heat-treated amyloid vehicle), single dose	50	100%, 6 dpt	EXP: 250 L tank	Sudová et al. (2010)
Senga sp.	*Channa micropletes*	B, 3 h	1	100%	EXP	Lewbart and Gratzek (1990)

B. acheilognathi remained viable after treatments that killed the adult tapeworm (Kline et al., 2009).

PZQ shows efficacy against *Eubothrium crassum* in rainbow trout (Mitchell, 1993) and the FAO recommend using PZQ and fenbendazole as treatments for infection by *Eubothrium* sp. in salmon (Jones, 2004). *Eubothrium* spp. have been recognised as a problem in salmon farming in Norway for decades (Bristow and Berland, 1991a, 1991b; Mitchell, 1993; Saksvik et al., 2001a, 2001b; Noga, 2010), and PZQ is used widely in Norwegian fish farming; however, there is only limited information on its application (NIPH, 2016). The recommended dose is 5 mg/kg BW for 2 days orally in feed (FHF, 2006; Lunestad et al., 2015). The low dose rate, and implied low dietary inclusion level, indicates palatability should not be an issue when treating this parasite. There have been reports of reduced efficacy of PZQ treatment when treating salmon for *Eubothrium* infections in Norway, indicating the development of resistance (FHF, 2006, 2008).

4.2. Digeneans

Digeneans, known as flukes, have a complex and diverse, indirect life cycle, and most are endoparasites. Digeneans are common in wild fish, where infections are usually asymptomatic, while unless the intermediate host—commonly aquatic snails, although sometimes fish—is present, they are uncommon in cultured fish (Noga, 2010). Adult parasites in fish are usually found in the intestine, though some, such as Aporocotylids (blood flukes) reside in the cardiovascular system. With the exception of *Cardicola* (see below), infections do not generally cause significant problems unless they occur in large numbers. Metacercaria (larval stage) in the flesh or skin can reduce the market value of fish, while in some cases can negatively impact fish health and lead to economic losses (Noga, 2010; Ogawa, 2015). Where mammals are definitive hosts, consumption of metacercaria in uncooked fish can result in food-borne zoonosis in humans (reviewed in Keiser and Utzinger, 2004).

Infections with *Cardicola* are a primary health concern in ranched Southern bluefin tuna (Nowak, 2004; Neumann et al., 2018) and farmed Pacific bluefin tuna (Shirakashi et al., 2012b), and can inflict significant losses on tuna aquaculture (the effects of *Cardicola* spp. on tuna aquaculture are discussed further in Balli et al., 2016). Juvenile Pacific bluefin tuna up to one year old are most threatened by *Cardicola* spp. and blood fluke-associated mortality can be greater than 50% (Shirakashi et al., 2012a; Ishimaru et al., 2013). Oral administration of PZQ has been shown to be very effective in treating infections in tuna with up to 100% clearance reported following oral dosing from as low as 7.5 mg/kg BW for 3 days (Hardy-Smith et al., 2012; Shirakashi et al., 2012a; Ishimaru et al., 2013). This low PZQ dose means that there are no palatability issues. PZQ shows efficacy *in vitro* for cercariae and even sporocysts of *Cardicola orientalis* (Shirakashi unpublished data). However, reinfection can occur, so if tuna remain exposed to the parasites infective stage retreatment is required; Pacific bluefin tuna may need to be treated 3–5 times within the first half year in cages. Additionally, while very effective against adult flukes, PZQ is not efficacious against eggs or miracidia, with eggs in gills remaining viable following treatment (Shirakashi et al., 2012a).

While intubation with PZQ was used in initial experiments with Southern bluefin tuna (Hardy-Smith et al., 2012) this is not practical for use on an industrial scale and treatment with medicated feed is used. In

Table 2
Use of PZQ in aquaculture against digeneans. B – bath, O – oral, I - intubation, Inj - injection. EXP – experiment, COM – commercial.

Parasite	Fish species	Delivery	Dose (mg kg^{-1} for oral, injection or intubation; mg L^{-1} for bath)	Efficacy dpt – days post treatment	EXP or COM	Reference
Cardicola forsteri	*Thunnus maccoyii*	O; I for 1 d, 27 d post-transfer to ranching pontoon	75 150	95%, 24 dpt 91%, 24 dpt	COM: ranching pontoon	Hardy-Smith et al. (2012)
Cardicola forsteri, Cardicola orientalis	*Thunnus maccoyii*	O; injected in baitfish for 2 d, 4–5 w post-transfer	30/d	Not applicable	COM	APVMA (2018)
Cardicola forsteri	*Thunnus maccoyii*	O, treated week 2 of ranching O, treated week 6 of ranching	15/d	75–94% at 12 wpt 94–~100% at 12 wpt	COM: ranching pontoon	Power et al. (2019)
Cardicola spp. (and other *Aporocotylidae*)	*Thunnus maccoyii* (and other Thunninae)	O; injected in baitfish for 2 d, 3–8 w post-transfer	15–30/d	Not applicable	COM	APVMA (2020c)
Cardicola opisthorchis, Cardicola orientalis	*Thunnus orientalis*	O; in feed (semi-defrosted Japanese sand lance) for 3 d	15/d	100%, 11 dpt	EXP: 6 × 6 m net cage	Shirakashi et al. (2012a)
Cardicola opisthorchis	*Thunnus orientalis*	O: in feed (semi-defrosted Pacific sand lance) for 3 d	7.5/d	100%	EXP: 6 × 6 × 4 m sea cage	Ishimaru et al. (2013)
Clinostomum complanatum	*Morone chrysops* × *M. saxatili*	B, 4 h B, 8 h B, 24 h	4 8 0.25	77.1%, 7 dpt 93.9%, 7 dpt 100%, 7 dpt	EXP: 80 L tank EXP: 5 or 80 L tank	Mitchell (1995)
Clinostomum complanatum	*Carassius auratus*	O; in feed for 3 d	138/d	100%	EXP: 40 L tank	Arakawa et al. (2021)
Clinostomum marginatum	*Ictalurus punctatus*	B, 24 h Inj; into muscle tissue below the posterior edge of the dorsal fin, single dose	0.65 + 15 mg/kg of fish 25	81%, 5.5 mpt 72%, 5.5 mpt	EXP: 3.35 × 0.76 × 0.52 m concrete vat EXP: 17 m^3 pool	Lorio (1989)
Clinostomum marginatum	*Ictalurus punctatus*	B, 2 h	2	100%, 21 dpt	EXP: 25 L tank	Plumb and Rogers (1990)
Diplostomum spathaceum	*Salmo gairdneri*	O; in feed (dry pellets) for 7 d O; in feed (dry pellets) every 4 d for 1 month	330/d 330/d	66.8–92.2%, 140 dpt 92.0–97.6%, 180 dpt	EXP: 1 × 1 m tank	Bylund and Sumari (1981)
Diplostomum spathaceum	*Ictalurus punctatus*	B, 2 h	2	93%, 21 dpt	EXP: 25 L tank	Plumb and Rogers (1990)
Diplostomum spathaceum	*Ctenopharyngodon idella*	O; in feed (mixed in pellets) for 1 d B, 20 min B, 1 h B, 90 h	330 50 10 1	100% 94.4%, 10 dpt 92.2%, 10 dpt 100%, 0 dpt	EXP: 50 L tank	Székely and Molnár (1991)
Diplostomum spathaceum	*Hypophthalmichthys molitrix*	B, 20 min B, 1 h B, 90 h	50 10 1	96.8%, 10 dpt 93.4%, 10 dpt 99.8%, 0 dpt	EXP: 50 L tank	Székely and Molnár (1991)
Diplostomum spathaceum	*Barbus*	B, 4 d	10	100%	EXP: 20 L tank	Zuskova et al. (2018)
Galactosomum sp.	*Seriola quinqueradiata*	O; in feed (coated on feed pellets) for 3 d	50/d	not stated	COM: 9 × 9 × 10.5 m net pen	Ido et al. (2019)
Nanophyetus salmincola	*Oncorhynchus tshawytscha*	Inj; intramuscular, single dose O; force fed (capsule/solution) for 1 d	20 100	ineffective ineffective	EXP: 1 × 8 × 0.3 m tank	Foreyt and Gorham (1988)
Posthodiplostomum minimum	*Lepomis macrochirus*	Inj; in epaxial muscle lateral to the dorsal fin, single dose	5	~100%, 14 dpt	EXP: tank	Bader et al. (2018)

Australia, PZQ is injected into freshly caught sardines *Sardinops sagax* and fed to ranched Southern bluefin tuna at 15–30 mg/kg BW for 2 days (Ellis and Kiessling, 2016; APVMA, 2018, 2020c). In Japan, where the use of PZQ against *C. opisthorchis* was approved in 2015, the effective dose is listed as 15 mg/kg BW for 3 days, and is delivered in feed mixed in defrosted bait fish and dry pellets (Shirakashi et al., 2012a; Ishimaru et al., 2013).

The Australian Southern bluefin tuna industry has utilised PZQ since early 2013, and this coincides with lower mortalities, reported at < 1%, compared to 10–15% in previous years (Dennis et al., 2010; Polinski et al., 2013; Neumann et al., 2018). While not all pontoons are treated due to economic considerations (Power et al., 2019), this may have a beneficial effect, the refugia of untreated flukes maintaining a population of susceptible parasites which may slowdown the development of PZQ resistance (Alsaqabi and Lotfy, 2014; Power et al., 2020). Later treatment during ranching (at 6 weeks as opposed to 2 weeks post-transfer), has been suggested as an effective method for controlling adult *Cardicola forsteri*, allowing for a longer Southern bluefin tuna ranching period (Power et al., 2019).

Other blood fluke infections of farmed fish treated with PZQ include *Paradeontacylix* spp. in *Seriola* spp. and unidentified aporocotylid from *Scomberomorus niphonius* (Nagano et al., 2013; Shirakashi and Ogawa, 2016; Shirakashi, pers. comms.).

PZQ is effective at treating juvenile stages of digeneans in fish, with treatment used to avoid detrimental health impacts, maintain market value, or to disrupt the parasites life cycle (Bader et al., 2017a). Treatment by oral, bath and injection are effective under different conditions.

PZQ bath treatments have been shown to remove up to 100% of *Clinostomum.* spp. in catfish and bass at concentrations starting from 0.25 mg/L (Lorio, 1989; Plumb and Rogers, 1990; Mitchell, 1995), while oral administration and injection have been shown to significantly reduce infections in goldfish and catfish, respectively (Lorio, 1989; Arakawa et al., 2021). PZQ is also very efficacious against *Diplostomum spathaceum*, with bath treatments shown to completely clear metacercaria from fish or larval forms from freshwater snails (Moser et al., 1986; Plumb and Rogers, 1990; Székely and Molnár, 1991; Voutilainen

Table 3
Use of PZQ in aquaculture against monogeneans. B – bath, O – oral, I - intubation, Inj - injection. EXP – experiment, COM – commercial.

Parasite	Fish species	Delivery	Dose (mg kg^{-1} for oral, injection or intubation; mg L^{-1} for bath)	Efficacy dpt – days post treatment	EXP or COM	Reference
Anacanthorus penilabiatus	*Piaractus mesopotamicus*	O; in feed 2 × per d for 7 d	30/d	not effective	EXP: 300 L tank	Schalch et al. (2009)
Anacanthorus penilabiatus	*Piaractus mesopotamicus*	B, 30 min	500	68.3%, 7 dpt	EXP: 500 L tank	Onaka et al. (2003)
Ancylodiscoides vistulensis	*Silurus glanis*	B, 5 h	10	15% prevalence reduction, 3–4 dpt	EXP: 10 L tank	Székely and Molnár (1990)
Benedenia seriolae	*Seriola lalandi*	B, 48 h, 7 w post-catch	2.5	100%	EXP: 400 L tank	Sharp et al. (2004)
Benedenia seriolae	*Seriola lalandi*	O; in feed (surface-coating feed pellets) for 6 d	75/d	66.4%, 4 dpt	EXP: 1.5 m sea cage	Williams et al. (2007)
		O; I for 3 d	150/d	97.7%		
Benedenia seriolae	*Seriola quinqueradiata*	O; I, single dose	450	78%	EXP: 3.375 m^3 sea cage	Williams (2009)
Benedenia seriolae	*Seriola lalandi*	O; I for 3 d	150/d	70%	EXP: seawater raceway	Williams (2009)
		O; I for 3 d	75/d + 200/d cimetidine	41%		
Benedenia seriolae	*Seriola quinqueradiata*	O; in feed (pellets) for 3 d, 15 d after parasite exposure	150/d	100% (large fish), 76.7% (small fish)	EXP: 100–1000 L tanks	Hirazawa et al. (2013)
Benedenia seriolae	*Seriola dumerili*	O; in feed (pellets) for 3 d, 15 d after parasite exposure	150/d	100% (large fish), 93% (small fish)	EXP: 100–1000 L tanks	Hirazawa et al. (2013)
Benedenia seriolae	*Seriola lalandi*	O; in feed (microcapsules surface-coated) for 7 d	64/d	100%	EXP: 5 m^3 tank	Partridge et al. (2014)
Benedenia seriolae	*Seriola lalandi*	O: I (moist pellet) for 3 d	165/d	100%	EXP: 1000 L flow tank	Forwood et al. (2016b)
		O: in feed (moist pellet) for 3 d. Fish stocking density of 3 kg/m^3	70/d	81.6%, 2 dpt	COM: 16 × 7 m sea cage	
Benedenia seriolae	*Seriola lalandi*	B, 30–60 min	2.5	Not applicable	COM	APVMA (2020b)
Benedenia lutjani, Benedenia rohdei	*Lutjanus carponotatus*	B, 2 × 2 h, within 48 h	20	100%	EXP: tank	Whittington and Ernst (2002)
Benedeniella posterocolpa	*Rhinoptera bonasus*	B, 90 min	20	100%, 2 dpt	EXP: 170 L tank	Thoney (1990)
Cleidodiscus sp.	*Pomoxis nigromaculatus*	B, 24 h	1.5	incomplete removal, >80%	EXP: 20 gallon tank	Bader et al. (2017b)
Clemacotyle australis	*Aetobatus narinari*	O: in feed (inside food fish) for 1 d	40	no effect	EXP: 1.5 M L tank	Janse and Borgsteede (2003)
		B, 45 min	25	100%		
Dactylogyrus intermedius	*Carassius auratus*	B, 48 h	13.5	93.3%, 6 dpt	EXP:	Zhang et al. (2013)
Dactylogyrus extensus	*Cyprinus carpio*	B, 180 min	5	100%	EXP: 2 L tank	Schmahl and Mehlhorn (1985)
Dactylogyrus vastator	*Cyprinus carpio*	B, 90 min	10	"most worms killed"	EXP: 2 L tank	Schmahl and Mehlhorn (1985)
		B, 180 min	5	100%		
Dactylogyrus vastator	*Carassius auratus*	B, duration not specified	20	80.3%	EXP: 20 L tank	Zhang et al. (2014)
Dactylogyrus sp.	*Poecilia reticulata*	B, 24 h	3	100%	EXP: 12 L tank	Fridman et al. (2014)
Dactylogyrus sp.	*Ctenopharyngodon idella*	B, 48 h	7.5	100%	EXP: 1500 L tank	Hoai and Van (2014)
Diplectanum oliveri	*Argyrosomus japonicus*	B, 2 h	20	100% of adults	EXP: 70 L tank	Joubert (2012)
Gyrodactylus aculeati	*Gasterosteus aculeatus*	B, 2 h	20	100%	EXP: 2 L tank	Schmahl and Taraschewski (1987)
		B, 16 h	10	100%		
Gyrodactylus sp.	*Oncorhynchus mykiss*	B, 3 h	10	97.7%	EXP: 10 L tank	Santamarina et al. (1991)
Gyrodactylus salaris	*Oncorhynchus mykiss*	O; in feed for 10 d	800/d	39% prevalence reduction	EXP: 80 L tank	Tojo and Santamarina (1998)
Gyrodactylus turnbulli	*Poecilia reticulata*	B, 24 h	3	89.1%	EXP: 12 L tank	Fridman et al. (2014)
Gyrodactylus turnbulli	*Poecilia reticulata*	B, 24 h	3	78–100%	EXP: 200 L tank	Levy et al. (2015)
Haliotrema abaddon	*Glaucosoma hebraicum*	B, 24 h	2	~97%	EXP: 120 L tank	Stephens et al. (2003)
Heteraxine heterocerca	*Seriola quinqueradiata*	O; intubation (paste) for 3 d	50/d	100%	EXP: 3.375 m^3 sea cage	Williams (2009)
Heterobothrium okamoti	*Takifugu rubripes*	O; in feed (feed pellets) for 20 d	40/d	67.2%	EXP: 100 L tank	Hirazawa et al. (2000)

(*continued on next page*)

Table 3 (*continued*)

Parasite	Fish species	Delivery	Dose (mg kg^{-1} for oral, injection or intubation; mg L^{-1} for bath)	Efficacy dpt – days post treatment	EXP or COM	Reference
Heterocotyle tokoloshei	*Dasyatis brevicaudata*	B, 12 h	20	incomplete parasite removal	EXP: 4000 L tank	Vaughan and Chisholm (2010)
		O; I, single dose	150	100%, 10 dpt		
Hexabothriidae	*Aetobatus narinari*	O: in feed (inside food fish) for 1 d	40	no effect	EXP: 1.5 M L tank	Janse and Borgsteede (2003)
		B, 45 min	25	100%		
Lepidotrema bidyana	*Bidyanus*	O: in feed (surface coated feed pellets) for 6 d	75/d	79% of adult, 64% of juveniles	EXP: 500 L tank	Forwood et al. (2013a)
		B, 48 h	10	99% of adults, 84% of juveniles		
Lepidotrema bidyana	*Bidyanus*	B, 60 min	40	77%	EXP: 50 L tank	Forwood et al. (2013b)
Ligictaluridus floridanus	*Ictalurus punctatus*	B, 3 × 3 h, each 72 h apart	10	96%	EXP: 80 L tank	Benavides-González et al. (2014)
Merizocotyle icopae Neoheterocotyle rhinobatidi Neoheterocotyle rhynchobatis Troglocephalus rhinobatidis	*Rhinobatos typus*	B, 2 × 40 h, 48 h apart	5	100%	EXP: 50 L tank	Chisholm and Whittington (2002)
Microcotyle sebastis	*Sebastes schlegeli*	O; I, single dose	200	100%	EXP: 50 L tank	Kim et al. (1998)
Microcotyle sebastis	*Sebastes schlegeli*	O; in feed (pellets) alternate days for 5 d	200/d	~59%	EXP: 2 × 2 × 5 m net pen	Kim and Cho (2000)
		B, 4 min	100	~99.5%		
Microcotyle sebastis	*Sebastes schlegeli*	O; I, single dose	200	92.3%	EXP: 50 L tank	Kim et al. (2001b)
			200 + 200 cimetidine	100%		
Microcotyle sebastis	*Sebastes schlegeli*	O; I, single dose	200	~98%	EXP: 50 L tank	Kim and Kim (2002)
			100 + 100 cimetidine	~97%		
Neobenedenia girellae	*Verasper variegatus*	O; in feed (pellet) for 11 d	40/d	65%	EXP: 100–500 L tank	Hirazawa et al. (2004)
Neobenedenia girellae	*Scomber japonicus*	O; in feed (semi-defrosted frozen krill) for 3 d, 33–35 or 39–41 dpt	150/d	>81.4%	COM: 4 × 4 m sea cages	Yamamoto et al. (2011)
Neobenedenia girellae	*Seriola quinqueradiata*	O; in feed (pellets) for 3 d	150/d	76% (large fish), 36% (small fish)	EXP: 100–1000 L tank	Hirazawa et al. (2013)
Neobenedenia girellae	*Seriola dumerili*	O; in feed (pellets) for 3 d	150/d	25% (large fish), 19% (small fish)	EXP: 100–1000 L tank	Hirazawa et al. (2013)
Neodermophthirius harkemai	*Negaprion brevirostris*	O; for 3 d	19/d	no effect	EXP: 2.5 M L tank	Poynton et al. (1997)
		Inj, intramuscular, single dose	7.5	no effect		
Pseudodactylogyrus anguillae	*Anguilla*	B, 25 h	10	100%	EXP: 17 L tank	Buchmann et al. (1990, 1993)
Pseudodactylogyrus anguillae	*Anguilla*	B; 24 h	5	95–100%	EXP: 6 L tank	Buchmann et al. (2011)
Sparicotyle chrysophrii	*Sparus aurata*	O; in feed (pellets) for 6 d	200/d	Prevalence reduced to 40%	EXP: 250 L tanks	Sitjà-Bobadilla et al. (2006)
Zeuxapta seriolae	*Seriola lalandi*	B; 48 h, 7 w post-catch	2.5	100%	EXP: 400 L tank	Sharp et al. (2004)
Zeuxapta seriolae	*Seriola lalandi*	O; in feed (surface-coated feed pellets) for 6 d	50/d	81.4%	EXP: 1.5 m sea cage	Williams et al. (2007)
		O; I for 6 d	50/d	100.0%		
Zeuxapta seriolae	*Seriola lalandi*	O; intubation for 3 d	150/d	100%	EXP: seawater raceway	Williams (2009)
			150/d + 200/d cimetidine	99.8%		
Zeuxapta seriolae	*Seriola lalandi*	O; in feed (microcapsules surface-coated) for 7 d	64/d	100%	EXP: 4 m^3 tank	Partridge et al. (2014)
Zeuxapta seriolae	*Seriola lalandi*	O I (moist pellet) for 3 d	45/d	100%	EXP: 1000 L flow tank	Forwood et al. (2016b)
		O; in feed (moist pellet) for 3 d. Fish stocking density of 3 kg/m^3	70/d	99.4%	COM: 16 × 7 m sea cage	
Zeuxapta seriolae	*Seriola lalandi*	O; in feed (moist pellet) for 3 d	70/d	Not applicable	COM	APVMA (2020a)
Zeuxapta seriolae	*Seriola lalandi*	B; 30–60 min	2.5	Not Applicable	COM	APVMA (2020b)
Zeuxapta seriolae	*Seriola dumerili*	O; in feed (pellets) for 3 d	150	80.4%	EXP: 3 m3 cage	Rigos et al. (2021)

et al., 2009; Zuskova et al., 2018). Additionally, oral treatments at 330 mg/kg BW of rainbow trout, *Oncorhynchus mykiss,* grasscarp *Ctenopharyngodon idella* and silver carp *Hypophthalmichthys molitrix* can result in 100% clearance after a single dose (Bylund and Sumari, 1981; Székely and Molnár, 1991). Further, a degree of prophylactic protection has been observed following treatment. Similar to other cases of prophylaxis reported following oral treatments (Hirazawa et al., 2000; Williams et al., 2007, 2009), this only lasts a few days, reflecting the

pharmacokinetics of PZQ, where even at high doses PZQ is completely eliminated from fish within 1 week (Bylund and Sumari, 1981; Kim et al., 2001a, 2003).

Several other juvenile digeneans have been effectively treated with PZQ (see Table 2), including *P. minimum* in bluegills (Bader et al., 2017a), and *Galactosomum* sp. in juvenile Japanese amberjacks (Ido et al., 2019).

4.3. Monogeneans

Monogeneans are generally ectoparasitic. Monopisthocotylean monogeneans usually feed on superficial layers of the skin and gills, while polyopisthocotyleans tend to infect the gills and primarily feed on blood (Noga, 2010; Hoai, 2019). The direct life cycles of monogeneans enable them to accumulate in aquaculture, where intensive levels of infections can cause considerable pathogenicity and economic losses (Reed et al., 2019; Ogawa, 2015).

PZQ has been shown to be highly effective against both monopisthocotyleans (e.g. Sharp et al., 2004; Williams et al., 2007; Forwood et al., 2013a, 2016b; Fridman et al., 2014) and polyopisthocotyleans (e.g. Kim et al., 1998, 2001b; Hirazawa et al., 2000; Kim and Cho, 2000; Partridge et al., 2014). However, several factors must be considered to ensure the most effective treatment, including dose, mode of delivery, treatment duration, and need for retreatment, with consideration given to the type of monogenean and its life cycle.

Higher PZQ doses are generally required to remove skin flukes compared to blood-feeding gill flukes. This reflects the higher levels of PZQ present in blood and increased PZQ exposure to blood-feeding gill flukes in contrast to those feeding on mucus and epithelial cells (Tubbs and Tingle, 2006a; 2006b). Orally delivered PZQ is more effective against polyopisthocotylean gill fluke *Heteraxine heterocerca* than against monopisthocotylean skin fluke *B. seriolae* (Williams, 2009). Additionally, PZQ bath treatment has been shown to be more effective against *Dactylogyrus* infecting the gills than *Gyrodactylus*, a skin fluke (Fridman et al., 2014).

As with most ectoparasites, bath treatments can work well and PZQ doses starting from 2 to 3 mg/L can be effective (see Table 3). Feed treatments can be effective; however, for some host-parasite combinations high doses are required, which can be difficult to achieve with oral applications due to palatability issues (Williams et al., 2007; Forwood et al., 2016b). Additionally, PZQ treatment does not always kill monogeneans and they can detach and survive for short periods and continue to produce viable eggs (Sharp et al., 2004; Hirazawa et al., 2013). The efficacy of PZQ against several monogeneans is described in more detail below.

Gyrodactylus salaris, which infests and lives on the body of Atlantic salmon and trout has been described as perhaps the most economically impactful ectoparasitic flatworm of fish (Blaylock and Bullard, 2014). PZQ bath treatments have generally been effective against several *Gyrodactylus* spp. (Schmahl and Taraschewski, 1987; Santamarina et al., 1991; Fridman et al., 2014; Levy et al., 2015). However, a high dose (800 mg/kg BW, 4% dietary inclusion level) oral treatment was ineffective at clearing *G. salaris* from rainbow trout, low palatability possibly affecting consumption (Tojo and Santamarina, 1998). There have been several reports that juvenile parasites are less susceptible to PZQ treatment (Schmahl and Taraschewski, 1987; Santamarina et al., 1991).

B. seriolae infests the skin (and sometimes the eyes) of *Seriola* spp. (Whittington, 2012) and is considered a significant risk to the sustainability and profitability of *Seriola* spp. culture industries (Ernst et al., 2002, 2005; Hutson et al., 2007; Hoai, 2019). Bath treatments can be 100% effective at removing *B. seriolae* from *S. lalandi* (Sharp et al., 2004); however, they can be stressful of fish and logistically difficult in sea-cage aquaculture so in-feed treatments have been pursued. The recommended treatment regimen for *B. seriolae* in Japan is oral administration of 150 mg/kg BW administered daily for three days. This dose delivered orally (intubation or in-feed) can achieve complete, or almost complete, clearance in *Seriola* spp. (Okabe, 2000; Williams et al., 2007; Hirazawa et al., 2013; Forwood et al., 2016b), though varying results have been reported, likely resulting from palatability issues (Williams et al., 2007, 2009; Forwood et al., 2016b).

B. seriolae eggs are refractory to PZQ (Sharp et al., 2004), while some oral PZQ treatments of *S. lalandi* have shown less efficacy against juvenile *B. seriolae* (Williams, 2009; Forwood et al., 2016b). Rather than representing an innate reduced susceptibility to PZQ, the continued presence of juvenile flukes likely reflects their location on the host. Forwood et al. (2016b) noted that juveniles found post-treatment were predominantly located on the eye of the fish and hypothesised that these parasites only have limited exposure to PZQ due to the poor vasculature on the external surface of the eye, and that PZQ treatment is therefore likely to be ineffective and retreatment must be strategically timed to target migrating fluke.

Some monogeneans appear innately more susceptible to PZQ. Hirazawa et al. (2013) showed that of the two capsalid monopisthocotyleans *B. seriolae* and *Neobenedenia girellae*, *N. girellae* is less susceptible to the effects of PZQ. *N. girellae* are one of the few monogeneans for which complete removal has been difficult to achieve with PZQ treatment (Yamamoto et al., 2011; Hirazawa et al., 2013). Reduced susceptibility is observed following oral delivery of PZQ in several fish species, with limited efficacy (19–86%) treating *N. girellae* at 150 mg/kg BW for 3 days reported (Hirazawa et al., 2004, 2013; Yamamoto et al., 2011). Both immature and mature worms appear equally resistant to PZQ (Yamamoto et al., 2011) while the viability of *Neobenedenia* spp. eggs appears unaffected (Morales-Serna et al., 2018). The efficacy of PZQ treatment against *N. girellae* varies depending on the host fish species; with treatment found to be more effective for *S. quinqueradiata* than with *S. dumerili* (Hirazawa et al., 2013). This highlights the need to evaluate PZQ efficacy with the target parasite-host combination.

Z. seriolae, a polyopisthocotylean, attaches to the gill lamellae and feeds on the blood of *Seriola* spp. (Grau et al., 2003; Mansell et al., 2005; Hutson et al., 2007; Lia et al., 2007; Williams et al., 2007). As both *Z. seriolae* and *B. seriolae* infect *Seriola* spp., PZQ treatment efficacy of these parasites is often compared, and several studies have shown *Z. seriolae* is cleared more effectively (Williams et al., 2007; Forwood et al., 2016b). Baths at 2.5 mg/L for 24-h or longer are up to ~100% effective against *Z. seriolae* in *S. lalandi* (Sharp et al., 2004) as is intubation from doses as low as 45 mg/kg BW for 3 days (Williams et al., 2007, 2009; Forwood et al., 2016b). As *Z. seriolae* is more susceptible than some other monogeneans to PZQ, palatability issues associated with oral delivery are less of a problem, and in-feed delivery of 64–70 mg/kg BW for 3–6 days can achieve >99% clearance (Partridge et al., 2014; Forwood et al., 2016b). Like several other flatworm parasites, despite high efficacy against adults, *Z. seriolae* eggs remain viable after PZQ treatment (Sharp et al., 2004).

Microcotyle sebastis are polyopisthocotyleans that parasitise the gills of several fish species, mostly of the genus *Sebastes* (rockfish). The parasite has been responsible for high mortality rates among juvenile fish in the Korean aquaculture industry (Kim et al., 1998). PZQ can effectively treat *M. sebastis* infestations in juvenile cultured rockfish *Sebastes schlegeli*; but ensuring adequate dosing under conditions seen in aquaculture is vital, and as with some other parasites, repeated treatments are needed due to reinfection in the field (Kim et al., 1998). A 4-min bath at 100 mg/L is well tolerated by rockfish and very effective, removing >99% of parasites (Kim and Cho, 2000), while single treatment intubations at 200 mg/kg BW have been able to achieve up to 100% treatment efficacy (Kim et al., 1998, 2001b; Kim and Kim, 2002). However, a 3 day in-feed treatment at 200 mg/kg BW (2% dietary inclusion level) had less than 60% efficacy, and though feed intake issues were not reported, it is likely that palatability issues led to low dosing in some fish (Kim and Cho, 2000). One method shown to increase PZQ treatment efficacy is co-administration with cimetidine (Kim et al., 2001b; Kim and Kim, 2002). Cimetidine can affect the metabolism and elimination of PZQ, leading to higher PZQ levels in the blood of

mammals and fish (Jung et al., 1997; Kim and Kim, 2002). This addresses a potential limitation of PZQ which can sometimes lead to inadequately sustained PZQ levels.

While total clearance is often observed against adult monogeneans, several studies have shown juveniles to be less affected (Schmahl and Taraschewski, 1987; Chisholm and Whittington, 2002; Forwood et al., 2013a), and eggs of many monogeneans are resistant to the effects of PZQ (Thoney, 1990; Sharp et al., 2004; Sitjà-Bobadilla et al., 2006; Morales-Serna et al., 2018). This has implications for reinfections, notably for monogeneans that produce filamentous eggs which entangle in net cages and cause reinfection (e.g. Capsalidea and Mazocraeidea). Eggs often entangle in net-cages and present opportunities for subsequent infection. Consequently, removal of at least some of the eggs either through net cleaning or net changes is required to minimise post-treatment infection while subsequent treatments must be timed to remove the parasite before they mature (Sharp et al., 2004; Yamamoto et al., 2011). Along with those monogeneans already mentioned, PZQ has been shown through bath or oral treatments to effectively treat several other monogenean parasites (see Table 3).

5. Pharmacokinetics

The use of PZQ in food fish can lead to residues in fish, and public health authorities require safe drug withdrawal periods. In Australia, the limit of detection, 0.02 mg/kg, has been set as the maximum residue limit for PZQ in fish muscle (APVMA, 2019); this coincides with many jurisdictions which have no set limit, thus requiring PZQ levels to be below detection limits.

The pharmacokinetics of PZQ are largely similar in fish and mammals, though in fish metabolism may be slower, resulting in parasites being exposed to active drug for longer (Bjorklund and Bylund, 1987). In general, and similar to mammals, short blood circulation times in fish correlate with high metabolic rates (Brill et al., 2008). Japanese amberjack and rainbow trout have circulation times of 1.3 min and 1.9 min respectively (Brill et al., 2008), in comparison mice have a blood circulation time of only 15 s (Debbage et al., 1998). This more rapid circulation combined with the fact PZQ undergoes significant first-pass metabolism in the liver has been proposed to explain some of the difference between mammals and fish species (Partridge et al., 2019).

In fish, PZQ is rapidly absorbed with peak levels occurring in blood from 30 min following administration by intubation, while rapid metabolism results in elimination occurring within days (Bjorklund and Bylund, 1987; Tubbs and Tingle, 2006a; Ishimaru et al., 2013; Xie et al., 2015; Kogiannou and Rigos, 2021; Kogiannou et al., 2021). High doses of PZQ take longer to be eliminated. Kim et al. (2003) showed that PZQ was still detected in the skin of rainbow trout for up to 6 days when intubated with 400 mg/kg BW, but for only 3 days when intubated at 200 mg/kg BW. These results can inform withdrawal periods for this fish species; however, due to variations between fish species and dosing regimens, withdrawal times should be determined for each species.

Additionally, variations in the environment impact PZQ metabolism (Ishimaru et al., 2013; Xie et al., 2015). Following intubation, PZQ is absorbed more rapidly at higher temperatures by rainbow trout (Bjorklund and Bylund, 1987); while salinity can influence PZQ tissue distribution and concentration in grass carp, with plasma and tissue levels lower and PZQ more quickly eliminated when in brackish water compared to fresh water (Xie et al., 2015). Further, fish size may influence PZQ uptake, with differences in PZQ absorption in the gastrointestinal tract between small and large *Seriola* spp. suggested as an explanation for observations of reduced PZQ effectiveness among small fish (Hirazawa et al., 2013).

Bioavailability can be influenced by mode of delivery. A comparison of oral and intravenous administration of PZQ in *S. lalandi* showed peak plasma and skin concentrations were almost twice as high following intravenous delivery, though half-lives were similar and higher levels of PZQ were detected in plasma compared to the skin by both delivery methods (Tubbs and Tingle, 2006a; 2006b). In bath treatments the main route of absorption of PZQ is proposed to be through the gills, but a small amount may be absorbed via the skin (Kim et al., 2001a). A study in rockfish showed following bath treatment PZQ levels were approximately 10 times lower in muscle than plasma and were eliminated quicker (Kim et al., 2001a). Alternatively, following oral administration (either intubation or feed), PZQ concentrations tend to be at relatively similar levels in serum and muscles in several species, while higher levels are observed in the liver and kidneys (Bjorklund and Bylund, 1987; Ishimaru et al., 2013; Xie et al., 2015). Oral co-administration of PZQ with cimetidine or in nanoparticles has been trialled to increase PZQ bioavailability. Nanoparticles, despite showing promise in mammalian studies, did not improve bioavailability in yellowtail kingfish (Partridge et al., 2019). Alternatively, cimetidine co-administration led to higher PZQ levels in the blood of rockfish and enhance treatment efficacy against *M. sebastis* (Kim et al., 2001b; Kim and Kim, 2002). although no improvement was observed when treating *B. seriolae* in yellowtail kingfish (Williams, 2009).

Ensuring chemical residue levels are below accepted thresholds is vital to ensuring consumer safety and maintaining consumer confidence in the industry. A range of factors can influence PZQ pharmacokinetics in fish; this variability means the fate of PZQ should be contemplated in regard to each species under relevant conditions. This needs to be considered both by authorities when stipulating withdrawal periods and by producers to ensure PZQ levels are below prescribed limits.

6. Development of resistance to PZQ

Development of resistance to effective drug treatments is a major threat to the future control of parasites. PZQ has been used widely to treat schistosomiasis and other flatworm infections in humans and other mammals for over 40 years, and during this time widespread resistance to PZQ has not emerged. This may be due to potential multiple targets and receptors for PZQ (Thomas and Timson, 2020).

Schistosomes with reduced sensitivity to PZQ have been generated in the laboratory (Fallon and Doenhoff, 1994; Coeli et al., 2013), and while schistosomes tend to exhibit reduced susceptibility rather than outright resistance to PZQ, there have been several reports in the literature of reduced efficacy of PZQ treatment of human schistosomiasis in the field (reviewed in Greenberg and Doenhoff, 2017). Reduced susceptibility to PZQ has not been limited to schistosomes, with reports of low cure rates of *C. sinensis* infections in Vietnam (although a low dose was prescribed) (Tinga et al., 1999; Chai, 2013), multiple PZQ treatments failing to cure tapeworm *Taenia saginata* infections in India (Lateef et al., 2008), and resistance reported in the zoonotic cestode *Dipylidium caninum* in dogs (Jesudoss Chelladurai et al., 2018).

It is widely recognised that the exposure of parasites to subtherapeutic doses of medicine promotes the development of parasite resistance. This is demonstrated with PZQ, whereby schistosomes with reduced susceptibility to PZQ were generated in the laboratory by exposing snails harbouring the parasite to low doses of PZQ (Couto et al., 2011). Obviously, this is relevant to aquaculture—if fish are not dosed properly parasites can be exposed to suboptimal doses. Additionally, the release of PZQ bath treatments or overfeeding in sea-cages, can result in the spread of PZQ into the environment.

While PZQ has been used in aquaculture in Japan since 2000 we are not aware of reports of any reductions in PZQ treatment efficacy against *B. seriolae* infections. This may be due, at least in part, to PZQ not being a common treatment method for skin fluke in Japan. By contrast, in Norway where PZQ has been used as an in-feed treatment of tapeworm infections of Atlantic salmon, *Eubothrium* sp., has developed resistance to PZQ (FHF, 2006, 2008). *Eubothrium* spp. cause major losses to Norwegian aquaculture (Saksvik et al., 2001a). No good alternative to PZQ has been found to date. While fenbendazole, which is now used, is efficacious against *Eubothrium* spp., it can have significant negative side-effects, including decreased appetite during and after treatment and

increased mortality, and is not recommended for use below 10 °C due to increased side-effects (FHF, 2006, 2008; O'Brien, 2012). As a result, the industry is now faced with using a treatment that does not always work or one that causes serious side-effects and is now required to invest in finding ways to better deal with the parasite.

Recent developments evaluating PZQ binding to the $TRPM_{PZQ}$ of schistosomes and *Fasciola* — PZQ susceptible and resistance organisms, respectively — have identified single amino acid changes that can ablate or confer responsiveness to PZQ (Park et al., 2021). This hints that PZQ effectiveness against platyhelminths may be sensitive to a single mutation, highlighting the possible ease with which reduced PZQ efficacy could evolve.

While not widespread, the limited development of reduced susceptibility to PZQ to date highlights that over-reliance on a single drug can become problematic. Especially in the case of PZQ, which along with use in aquaculture is the first-choice treatment for cestodes and trematodes infections in humans and animals. Those using PZQ need to be aware of the potential for resistance to develop among parasites, and that monitoring should be undertaken, and alternative strategies prepared. One way suggested to slowdown resistance development is to leave some parasites untreated, i.e. worms in refugia, which maintains a population of susceptible parasites (van Wyk, 2001; Hodgkinson et al., 2019). PZQ use as a component of integrated pest management, that considers parasite life cycles such as those outlined by Huston et al. (2020), can ensure maximum treatment efficiency and facilitate long term effectiveness.

7. Side effects and toxicity of PZQ

Only a limited number of toxicity studies have been undertaken, with PZQ sensitivity shown to vary between fish species. The 96-h median lethal concentrations (LC50) for grass carp *Ctenopharyngodon idella*, juvenile North African catfish *Clarias gariepinus* and golden shiners *Notemigonus crysoleucas* ranged from 50 to 61 mg/L (Mitchell and Hobbs, 2007; Nwani et al., 2014), while barbels and goldfish were more sensitive to PZQ, with 96-h LC50 of 28.6 mg/L and 29.2 mg/L, respectively (Zhang et al., 2014; Zuskova et al., 2018). Some fish species, including clupeoids, appeared to be more sensitive to PZQ (Thoney and Hargis, 1991; Obiekezie and Okafor, 1995). *Argyrosomus japonicus* died within 18 h when exposed to PZQ solution at 20 mg/L and showed signs of stress upon exposure to 2 mg/L (Joubert, 2012). Additionally, some juvenile fish were more sensitive (Thoney and Hargis, 1991). *C. gariepinus* fry had a 24-h LC50 of just 13.4 mg/L and mortalities were observed by 48 h at PZQ concentrations as low as 3.5 mg/L (Obiekezie and Okafor, 1995).

Nwani et al. (2014) proposed that PZQ had neurotoxic properties to explain the range of adverse reactions, including fish mortalities, that have occurred in some bath studies. Eels can become paralysed within 1 min at PZQ concentrations above 600 mg/L and within 18 min at 120 mg/L, while a range of adverse effects, including impaired swimming, swimming upside down, loss of equilibrium, respiratory distress, and bursts of hyperactivity have been reported in a number of fish species during PZQ bath treatments, although behaviours return to normal upon removal from treatment (Schmahl and Mehlhorn, 1985; Buchmann, 1987; Székely and Molnár, 1990, 1991; Janse and Borgsteede, 2003; Onaka et al., 2003; Joubert, 2012; Forwood et al., 2013b).

In general, the effective doses used to treat flatworm infections in fish are much lower than the levels that cause adverse effects. While some high concentration doses reported to be effective result in adverse effects, in many cases it has been shown that treatments for a longer duration at lower concentration are equally or more effective (Mitchell and Darwish, 2009). Mitchell and Hobbs (2007) demonstrated that bath treatments with low concentrations of PZQ can have a large safety margin (>30-fold).

Further, while no phenotypic changes or mortalities may be observed at effective treatment concentrations, long term sublethal doses (5.35 mg/L for 10 days) can elicit changes in catfish that indicate toxicity, such as micronucleus induction and alterations of haematological and biochemical parameters (Nwani et al., 2014). Changes in antioxidant biomarkers in the liver and muscle of barbels at therapeutic doses (10 mg/L) have been reported (Zuskova et al., 2018), as have minor haematological changes in Nile tilapia *Oreochromis niloticus* exposed to 40–60 mg/kg BW for up to 96 h (El-Banna et al., 2008) and common carp *Cyprinus carpio* intubated with 30–50 mg/kg BW (Sudová et al., 2009).

Oral applications of PZQ have a wide safety margin with few side effects. Even large oral PZQ doses did not result in toxicity to fish; for example, no adverse effects were reported in rainbow trout administered 500–800 mg/kg BW (Bjorklund and Bylund, 1987; Tojo and Santamarina, 1998) or Japanese amberjack up to 450 mg/kg BW (Williams, 2009). Adverse effects have not been reported following injections in several fish species at therapeutic concentrations from 5 to 25 mg/kg BW (Foreyt and Gorham, 1988; Lorio, 1989; Poynton et al., 1997; Bader et al., 2018); however, mortality has been recorded in *S. lalandi* post-administration of a 100 mg/kg BW intravenous dose (Tubbs and Tingle, 2006b). Several fish species, such as Atlantic salmon and yellowtail kingfish, show no toxic effects when exposed to PZQ levels several fold higher than the recommended dose (Lunestad et al., 2015; Forwood et al., 2016a), and no haematological or biochemical indices indicated stress in *S. lalandi* intubated with 500 mg/kg BW (Forwood et al., 2016a).

Following treatment of Schistosomiasis in humans, the severity of some adverse events correlate with infection intensity and are due to dying parasites and the body's response (Polderman et al., 1984; Stelma et al., 1995). The potential for mortalities in fish linked to PZQ's action on internal parasites exists. Mass mortalities in goldfish have been linked to treatment with PZQ and trichlorfon, with drug treatment proposed to activate mass *C. complanatum* metacercaria excystment resulting in lethal damage to fish; treatment before metacercariae fully develop has been proposed to avoid this outcome (Arakawa et al. 2021).

In summary, even though PZQ is relatively safe, toxic levels can be reached in bath treatments. Additionally, some variation is seen in sensitivity to PZQ between fish species, so suitable treatment levels must be carefully ascertained for each species and life stage, while in some cases the timing of treatment may need to be considered to minimise detrimental impacts from dying parasites.

8. Persistence in the aquatic environment

It is important to understand how quickly PZQ degrades in the aquatic environment for several reasons, including treatment efficacy and to evaluate environmental implications. From a treatment perspective, when undertaking bath treatments, it is critical that dosing levels are maintained for the duration of the treatment to ensure efficacy; subtherapeutic levels can result in incomplete parasite removal, with implications on costs and fish health, and the potential development of PZQ resistance by the target parasite. Alternatively, following use in aquaculture, the release of PZQ into the aquatic environment can be problematic; leading to the development of resistance, while the possibility of effects on off-target species in the water column and sediment can have profound environmental implications.

In recent years there has been an increased focus on pharmaceuticals in the environment, and concentrations of antibiotics at elevated levels have been found in the vicinity of aquaculture farms (Cabello, 2006; Morley, 2009). However, while PZQ has been identified at low levels (7.8–15 μg/L) in wastewater, linked to its widespread use in human medicine and agriculture (Periša and Babić, 2014), little work has been done examining the persistence and effects of PZQ in the aquatic environment.

In general, treatments used in aquaculture, such as PZQ, have a high potential to reach the aquatic environment; although, release depends on how it is delivered and the aquaculture system in which it is used

(Crane et al., 2008). As a result of overfeeding or reduced appetite, medicated feed may not be eaten becoming available to the environment, and this is considered a major route of environmental contamination with aquaculture medications (Boxall et al., 2008). Alternatively, in sea-cages exploitative wild fish or crustaceans may take up feed. Additionally, following treatment PZQ can be excreted by fish (Bjorklund and Bylund, 1987), although the relatively efficient metabolism of PZQ and low activity of its metabolites is expected to limit this type of exposure. Following bath treatments, residual chemicals are either released into the surrounding water or diverted to local wastewater treatment (Grant, 2002). A more thorough review of the release of drugs used in aquaculture into the environment is given by Boxall et al. (2008) and Metcalfe et al. (2008).

Several factors, such as pH, oxidation, UV, and temperature can influence the stability of PZQ in the laboratory (Hashem et al., 2017). However, how this translates to PZQ degradation in specific aquatic environments has not been thoroughly studied and there is a lack of information concerning the fate and stability of PZQ following its use in aquaculture. PZQ degrades naturally, but variably, in marine aquaria, with PZQ levels sometimes dropping to below detection limits in as little as 2 days (Crowder and Charanda, 2004; Thomas et al., 2016). While this indicates PZQ can degrade in marine ecosystems, quick breakdown has been proposed to be dependent on the presence of microbial populations rather than an inherent instability of PZQ in seawater, as no drop in PZQ levels was observed after 15 days in a sterile system (Thomas et al., 2016). It should be noted that marine samples showed minimal degradation over 81 days when kept refrigerated (Crowder and Charanda, 2004).

Potential residue formation of PZQ in marine sediments has been studied. Delivery of PZQ as medicated feed in sea-cages is expected to result in the presence of PZQ in sediment (Hormazábal and Yndestad, 1995). Lunestad et al. (2015) reported only limited degradation of PZQ in seabed sediment over a month; a 50% reduction in PZQ levels in the top layer of sediment (<2 cm) and no reduction in a lower layer (5–7 cm). This persistence of PZQ in sediment would result in extended exposure to bottom-dwelling organisms. However, PZQ was below the detection limit (<0.01 mg/kg dry weight) in sediment taken from directly below sea-cages during and after PZQ treatments at an aquaculture site (Ido et al., 2019). Here, PZQ levels were monitored in a field setting during oral treatment of *S. quinqueradiata* at 50 mg/kg BW/day. PZQ was detected in surface water at low levels during treatment in the net pen (3 μg/L) and up to 30 m away (0.13 μg/L), but by 3 days post-treatment PZQ levels in the net pen had reduced significantly (0.08 μg/L) and were below detection levels (<0.1 μg/L) in surrounding water (Ido et al., 2019). Combined with no PZQ detected in sediments, the results suggested rapid dispersion and a lack of accumulation of PZQ in this setting.

In some scenarios, residual PZQ can be sent to waste treatment, however this method may not always eliminate PZQ prior to release into the environment (Periša and Babić, 2014; Marsik et al., 2017) and several methods for PZQ removal from waste water and the aquatic environment have been suggested, including phytoremediation (Marsik et al., 2017) and photodegradation (Havlíková et al., 2016; Cizmic et al., 2017). However, as relatively little work has been undertaken on monitoring PZQ release and its effects on the environment, it is not known if such treatments are necessary. Further studies on preferred disposal methods of PZQ-contaminated water, monitoring at aquaculture sites and evaluation of possible environmental risks are needed to better inform decisions in this area.

9. Effects on non-target species

Despite expected release of PZQ into the surrounding environment following its use in aquaculture, there are relatively few published reports on the ecotoxicological impacts of PZQ use. Levels of PZQ released following aquaculture may generally be expected to be relatively low and therefore it may be assumed that risks from acute toxicity in non-target species is low; however, the unintended outcomes caused by effects on non-target species should not be underestimated.

While there have been limited reports of resistance to PZQ developing, arguably the greatest risk posed by PZQ in the environment is the development of resistance. Subtherapeutic doses of drug have been shown to induce reduced susceptibility in *Schistosoma* hosted by snails. This risk extends to other platyhelminths, whether those targeted for treatment in aquaculture, or those in the surrounding environment that may be inadvertently exposed to residual PZQ.

The effects of PZQ on non-targeted platyhelminths in the aquatic environment is an obvious concern. PZQ is highly effective at killing both free-living and parasitic flatworms. PZQ has been shown to rid flatworms from coral aquaculture (Barton et al., 2021), while doses as low as 0.07 mg/L are effective at killing trematodes infecting some snails (Moser et al., 1986). Killing or exerting selective pressure on parasitic platyhelminths can have effects on host-parasite interactions. Parasitic platyhelminths can be common natural stressors of freshwater and marine organisms and can have significant effects on host physiology and population structure (reviewed in Morley, 2009). Additionally, turbellarians are free-living non-parasitic flatworms, some of which play an important role in watercourse ecosystems and are often very important as bio-indicators that influence food webs (Martens and Schockaert, 1986; Kolasa, 2000; Manenti and Bianchi, 2014).

Platyhelminths, along with a variety of other organisms are present in seabed sediments. This is an environment where PZQ has been shown to accumulate, resulting in the potential for extended exposure to bottom-dwelling organisms (Lunestad et al., 2015). Bottom-dwelling organisms are important in organic decomposition and sediment leaching, and toxic effects on these organisms can detrimentally affect these processes.

The consequences of PZQ in the environment does not just stem from killing flatworms. Planarians are capable of regenerating bodies when heads or tails are amputated. PZQ can disrupt this regeneration; when the planarian *Dugesia japonica* is exposed to PZQ, worms regenerate with two heads, with duplicated and integrated central nervous systems and organs (Nogi et al., 2009).

In addition to effects on flatworms, there is some evidence that PZQ is effective at treating some protozoan parasite infections, including *Giardia* sp., *Epistylis* sp., *Trichodina* sp., and *Entamoeba histolytica* (Flisser et al., 1995; Mohammad, 1998; Hoai and Van, 2014). This opens the possibility that PZQ may be capable of killing or detrimentally effecting protozoans that maintain the ecology of aquatic environments through their importance to food webs and nutrient recycling (Vickerman, 1992).

The effects of PZQ on certain molluscs, arthropods and plants has been reported. The infection intensity of parasitic Crustacea *Lernaea* sp. on common carp is reduced at PZQ concentrations greater than 2.5 mg/L after exposure for 48 h (Hoai and Van, 2014), while some estuarine snail species infected with trematodes have been reported to die after 10 days exposure to 0.89 mg/L (Moser et al., 1986). Alternatively, PZQ is well tolerated by the snail *Cornu aspersum* upon exposure to 1.8 mg per snail (equivalent to approximately 210 mg/kg/BW) to treat *Brachylaima* metacercariae (Gallego and Gracenea, 2015) and Lunestad et al. (2015) reported no toxic effects against a variety of marine bottom-dwelling organisms such as mussels, snails, crustaceans or polychaetes. Additionally, PZQ shows very low toxicity against the dung beetle *Aphodius constans*, with an LC50 > 1000 mg/kg, although larvae may change colour following exposure at high concentrations (Hempel et al., 2006). Alternatively, and of environmental significance, PZQ has lethal effects on the common earthworm *Lumbricus terrestris,* at levels (<11.5 mg/kg) that may be expected to be encountered in pastures grazed by treated animals (Goodenough et al., 2019). This is a vital keystone species involved in maintaining functional soil ecosystems.

PZQ's effects on plants vary. PZQ induced responses associated with stress and detrimentally affected growth of Thale cress *Arabidopsis*

thaliana at 1.5 mg/L (Landa et al., 2018). However, the common reed *Pragmites australis* exhibited no signs of stress when exposed to up to 200 mg/L of PZQ and was able to metabolise PZQ and remove it from water, suggesting a possible role in phytoremediation (Marsik et al., 2017).

While PZQ is considered specific against platyhelminths, a fact reinforced by the generally wide margin of safety observed when used as an anthelmintic treatment in fish and mammals, as outlined here several reports have detailed adverse effects from PZQ against organisms that are not platyhelminths. This has implications when assessing the environmental impact of PZQ. It also highlights the need for more extensive study to ascertain the true extent of the specificity and impact of PZQ on aquatic and terrestrial organisms.

10. Conclusions

PZQ has efficacy against a broad range of flatworm parasites and is used by the aquaculture industry to treat several parasites in different fish species. PZQ's high efficacy against several parasites of considerable importance, combined with its low toxicity and rapid metabolism and elimination from fish, presents it as a therapeutic that should continue to enjoy wide utility in aquaculture in coming years. While regulated for treatment of fish for human consumption with clear guidelines on use and withdrawal periods in several jurisdictions, PZQ enjoys a somewhat restricted regulatory environment and is used off-label under veterinary justification in certain parts of the world.

Variation exists regarding the efficacy of PZQ treatments. Certain parasites are more innately susceptible to PZQ, while mode of delivery and fish species also influencing treatment efficacy. To ensure PZQ can be optimally utilised by the aquaculture industry, further work is required to refine administration and dosage against a wider range of parasites, with specific emphasis on target host-parasite systems and safety in target fish species. To ensure PZQ remains a sustainable, effective control option, administration should ideally be informed by a knowledge of the target-parasites lifecycle and should be used in conjunction with other parasite management strategies to avoid development of parasite resistance to PZQ.

The current issues with palatability in feed are an obstacle that needs to be overcome before PZQ can be further embraced by the aquaculture industry. High PZQ treatment doses necessitating high dietary inclusion levels currently limit oral PZQ administration for treatment of certain parasites. As in feed delivery can be the most convenient form of administration in commercial aquaculture this represents an obvious problem. Bath treatments can represent a viable alternative; however, logistical complexity, costs and stress on fish can limit their utility in commercial settings. Feeding techniques, different formulations to mask taste, and methods to increase bioavailability have been trialled with only limited success and further work is needed to overcome this issue.

As with any medication used by the aquaculture industry, PZQ needs to be used in a prudent and responsible manner to minimise potential negative impacts. While often considered highly specific to flatworms PZQ can produce adverse impacts in other organisms and non-target species. The high probability of release of PZQ into the aquatic environment following use in aquaculture systems means monitoring for environmental impacts or resistance development is vital. Resistance to PZQ among *Eubothrium* sp. already impacts salmon farming in Norway, while the discovery that even a single mutation to TRP (the possible site of PZQ action in parasites) ablates responsiveness highlights the ease with resistance development may be possible. Further work needs to be done to better understand and address the environmental concerns and the ecological impacts of PZQ.

While PZQ is undoubtably an important component in some current aquaculture systems, and has potential to continue to be used by the aquaculture industry to treat a range of fish parasites, further work is required to ensure PZQ's potential is fully realised and it can remain a viable treatment option in the future.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgements

This review was made possible by funding to NJB by the Australian Government through the Fisheries Research and Development Corporation (FRDC2018-170).

References

Adnyana, W., Ladds, P.W., Blair, D., 1997. Efficacy of praziquantel in the treatment of green sea turtles with spontaneous infection of cardiovascular flukes. Aust. Vet. J. 75 (6), 405–407.

Alsaqabi, S.M., Lotfy, W.M., 2014. Praziquantel: a review. J. Vet. Sci. Technol. 5 (5), 1–8.

Andrews, P., Thomas, H., Pohlke, R., Seubert, J., 1983. Praziquantel. Med. Res. Rev. 3 (2), 147–200.

APVMA (Australian Pesticides and Veterinary Medicines Authority), 2018. Australian Pesticides and veterinary medicines authority. Permit 85738 Available at: https://portal.apvma.gov.au/permits. (Accessed 9 April 2020).

APVMA (Australian Pesticides and Veterinary Medicines Authority), 2019. Agricultural and Veterinary Chemicals Code (MRL Standard) Instrument 2019. *Amendment Instrument (No. 3) 2020,* compilation date 3 April 2020. Available at: https://www.legislation.gov.au/Details/F2020C00300. (Accessed 27 April 2020).

APVMA (Australian Pesticides and Veterinary Medicines Authority) (2020a). *Australian Pesticides and Veterinary Medicines Authority* Permit 87336. Available at: https://portal.apvma.gov.au/permits (accessed 9 April 2020).

APVMA (Australian Pesticides and Veterinary Medicines Authority) (2020b). *Australian Pesticides and Veterinary Medicines Authority* Permit 87833. Available at: https://portal.apvma.gov.au/permits (accessed 21 January 2021).

APVMA (Australian Pesticides and Veterinary Medicines Authority) (2020c). *Australian Pesticides and Veterinary Medicines Authority* Permit 88128. Available at: https://portal.apvma.gov.au/permits (accessed 21 January 2021).

Arakawa, J., Suzuki, K., Ishii, R., 2021. Seasonality of *Clinostomum complanatum* cercariae in the snail host *Radix auricularia japonica* and drug treatment of the parasite in goldfish *Carassius auratus*. Fish Pathol. 55 (4), 162–165.

ASEAN (Association of Southeast Asian Nations), 2013. *Guidelines for the Use of Chemicals in Aquaculture and Measures to Eliminate the Use of Harmful Chemicals*. Jakarta, ASEAN Secretariat. https://asean.org/?attachment_id=48796. (Accessed 21 March 2021).

Bader, C., Jesudoss Chelladurai, J., Starling, D.E., Jones, D.E., Brewer, M.T., 2017a. Assessment of *in vitro* killing assays for detecting praziquantel-induced death in *Posthodiplostomum minimum* metacercariae. Exp. Parasitol. 181, 70–74.

Bader, C., Jesudoss Chelladurai, J., Starling, D.E., Jones, D.E., Brewer, M.T., 2018. Efficacy of injectable praziquantel for elimination of trematode metacercariae in bluegills (*Lepomis macrochirus*) and quantification of parasite death by propidium iodide staining. Parasitol. Res. 117 (2), 365–370.

Bader, C., Jesudoss Chelladurai, J., Thompson, K., Starling, D., Brewer, M.T., 2017b. Outbreak of *Cleidodiscus* in juvenile black crappies (*Pomoxis nigromaculatus*) and bath treatment with praziquantel. J. Fish. Dis. 40 (11), 1737–1739.

Bader, C., Starling, D.E., Jones, D.E., Brewer, M.T., 2019. Use of praziquantel to control platyhelminth parasites of fish. J. Vet. Pharmacol. Therapeut. 42 (2), 139–153.

Bais, S., Greenberg, R.M., 2018. TRP channels as potential targets for antischistosomals. Int. J. Parasitol. Drugs Drug. Resist. 8 (3), 511–517.

Balli, J., Mladineo, I., Shirakashi, S., Nowak, B.F., 2016. Diseases in tuna aquaculture. In: Benetti, D.D., Partridge, G.J., Buentello, A. (Eds.), Advances in Tuna Aquaculture: from Hatchery to Market. Elsevier Inc., pp. 253–272

Barton, J.A., Neil, R.C., Humphrey, C., Bourne, D.G., Hutson, K.S., 2021. Efficacy of chemical treatments for *Acropora*-eating flatworm infestations. Aquaculture 532, 735978.

Bartsch, H., Kuroki, T., Malaveille, C., Loprieno, N., Barale, R., Abbondandolo, A., Bonatti, S., Rainaldi, G., Vogel, E., Davis, A., 1978. Absence of mutagenicity of praziquantel, a new, effective, anti-schistosomal drug, in bacteria, yeasts, insects and mammalian cells. Mutat. Res. Genet. Toxicol. 58 (2–3), 133–142.

Benavides-González, F., Gómez-Flores, R.A., Sánchez-Martínez, J.G., Rábago-Castro, J.L., Montelongo-Alfaro, I.O., 2014. *In vitro* and *in vivo* antiparasitic efficacy of praziquantel against monogenean *Ligictaluridus floridanus* in channel catfish (*Ictalurus punctatus*). Thai. J. Vet. Med. 44 (4), 533–539.

Benetti, D.D., Partridge, G.J., Buentello, A., 2016. Advances in Tuna Aquaculture: from Hatchery to Market. Elsevier, Amsterdam, 375pp.

Bjorklund, H., Bylund, G., 1987. Absorption, distribution and excretion of the anthelmintic praziquantel (Droncit) in rainbow trout (*Salmo gairdneri* R.). Parasitol. Res. 73 (3), 240–244.

Blaylock, R.B., Bullard, S.A., 2014. Counter-insurgents of the blue revolution? Parasites and diseases affecting aquaculture and science. J. Parasitol. 100 (6), 743–755.

Blumenthal, A.R., 2014. 'Using Garlic (*Allium sativum*) as a Masking Agent to Improve Palatability of Praziquantel-Medicated Feed for Juvenile Yellowtail Kingfish (*Seriola lalandi*)'. Masters Thesis. University of Miami.

Boxall, A., Crane, M., Corsing, C., Erikson, C., Tait, A., 2008. Uses and inputs of veterinary medicines in the environment. In: Crane, M., Boxall, A.B.A., Barrett, K. (Eds.), Veterinary Medicines in the Environment. CRC Press, Boca Raton, pp. 7–20.

Brill, R.W., Cousins, K.L., Jones, D.R., Bushnell, P.G., Steffensen, J.F., 2008. Blood volume, plasma volume and circulation time in a high-energy-demand teleost, the yellowfin tuna (*Thunnus atbacares*). J. Exp. Biol. 201, 647–654.

Bristow, G.A., Berland, B., 1991a. A report on some metazoan parasites of wild marine salmon (*Salmo salar* L.) from the west coast of Norway with comments on their interactions with farmed salmon. Aquaculture 98 (1), 311–318.

Bristow, G.A., Berland, B., 1991b. The effect of long term, low level *Eubothrium* sp. (Cestoda: *pseudophyllidea*) infection on growth in farmed salmon (*Salmo salar* L.). Aquaculture 98 (4), 325–330.

Buchmann, K., 1987. The effects of praziquantel on the monogenean gill parasite *Pseudodactylogyrus bini*. Acta Vet. Scand. 28 (3–4), 447.

Buchmann, K., 1993. Epidemiology and control of *Pseudodactylogyrus* infections in intensive eel culture systems: recent trends. Bull. Fr. Peche Piscic. 328, 66–73.

Buchmann, K., Kania, P.W., Neumann, L., De` Besi, G., 2011. Pseudodactylogyrosis in *Anguilla anguilla* (Actinopterygii: Anguilliformes: Anguillidae): change of control strategies due to occurrence of anthelmintic resistance. Acta Ichthyol. Piscatoria 41 (2), 105–108.

Buchmann, K., Székely, C., Bjerregaard, J., 1990. Treatment of Pseudodactylogyrus infestations of *Anguilla anguilla* II.: trials with bunamidine, praziquantel and levamisole. Bull. Eur. Assoc. Fish Pathol. 10 (1), 18–19.

Bylund, G., Sumari, O., 1981. Laboratory tests with Droncit against diplostomiasis in rainbow trout, *Salmo gairdneri* Richardson. J. Fish. Dis. 4, 259–264.

Cabello, F.C., 2006. Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment. Environ. Microbiol. 8 (7), 1137–1144.

Chai, J.Y., 2013. Praziquantel treatment in trematode and cestode infections: an update. Infect. Chemother. 45 (1), 32–43.

Chandiwana, S., Woolhouse, M., Bradley, M., 1991. Factors affecting the intensity of reinfection with *Schistosoma haematobium* following treatment with praziquantel. Parasitology 102 (1), 73–83.

Chisholm, L.A., Whittington, I.D., 2002. Efficacy of praziquantel bath treatments for monogenean infections of the *Rhinobatos typus*. J. Aquat. Anim. Health 14, 230–234.

Cizmic, M., Ljubas, D., Curkovic, L., Skoric, I., Babic, S., 2017. Kinetics and degradation pathways of photolytic and photocatalytic oxidation of the anthelmintic drug praziquantel. J. Hazard Mater. 323 (Pt A), 500–512.

Coeli, R., Baba, E.H., Araujo, N., Coelho, P.M., Oliveira, G., 2013. Praziquantel treatment decreases *Schistosoma mansoni* genetic diversity in experimental infections. PLoS Neglected Trop. Dis. 7 (12), e2596.

Couto, F.F., Coelho, P.M.Z., Araújo, N., Kusel, J.R., Katz, N., Jannotti-Passos, L.K., Mattos, A.C.A., 2011. *Schistosoma mansoni*: a method for inducing resistance to praziquantel using infected *Biomphalaria glabrata* snails. Mem. Inst. Oswaldo Cruz 106 (2), 153–157.

Crane, M., Boxall, A.B.A., Barrett, K., 2008. Veterinary Medicines in the Environment. CRC Press, Boca Raton.

Crowder, J., Charanda, T., 2004. Development and application of a method to detect and quantify praziquantel in seawater. In: 1st AQUALITY Symposium. Oceanario De Lisboa, Portugal.

Dayan, A.D., 2003. Albendazole, mebendazole and praziquantel. Review of non-clinical toxicity and pharmacokinetics. Acta Trop. 86 (2), 141–159.

Debbage, P.L., Griebel, J., Ried, M., Gneiting, T., DeVries, A., Hutzler, P., 1998. Lectin intravital perfusion studies in tumor-bearing mice: micrometer-resolution, wide-area mapping of microvascular labeling, distinguishing efficiently and inefficiently perfused microregions in the tumor. J. Histochem. Cytochem. 46 (5), 627–639.

Dennis, M.M., Landos, M., D'Antignana, T., 2010. Case-control study of epidemic mortality and *Cardicola forsteri*-associated disease in farmed southern bluefin tuna (*Thunnus maccoyii*) of South Australia. Vet. Pathol. 48 (4), 846–855.

Doenhoff, M.J., Coles, G.C., Pica-Mattoccia, L., Wheatcroft-Francklow, K., 2009. Chemotherapy and drug resistance in schistosomiasis, fascioliasis and tapeworm infections. In: Mayers, D.L., Sobel, J.D., Ouellette, M., Kaye, K.S., Marchaim, D. (Eds.), Antimicrobial Drug Resistance. Springer, pp. 629–646.

El-Banna, S., Zaghlol, N.F., Saad, T., 2008. The effects of praziquantel on selected hematological and biochemical indices in Nile Tilapia (*Oreochromis niloticus*) with tapeworm infestation. J. Arabian Aquacult. Soc. 3, 80–93.

Ellis, D., Kiessling, I., 2016. Ranching of southern bluefin tuna in Australia. In: Benetti, D. D., Partridge, G.J., Buentello, A. (Eds.), Advances in Tuna Aquaculture: from Hatchery to Market. Elsevier Inc., pp. 217–232

Ernst, I., Whittington, I.D., Corneillie, S., Talbot, C., 2002. Monogenean parasites in sea-cage aquaculture. Austasia Aquacult. 16, 46–48.

Ernst, I., Whittington, I.D., Corneillie, S., Talbot, C., 2005. Effects of temperature, salinity, desiccation and chemical treatments on egg embryonation and hatching success of *Benedenia seriolae* (Monogenea: Capsalidae), a parasite of farmed *Seriola* spp. J. Fish. Dis. 28 (3), 157–164.

Fallon, P.G., Doenhoff, M.J., 1994. Drug-resistant schistosomiasis: resistance to praziquantel and oxamniquine induced in *Schistosoma mansoni* in mice is drug specific. Am. J. Trop. Med. Hyg. 51 (1), 83–88.

Flisser, A., Sarti, E., Sarti, R., Schantz, P., Valencia, S., 1995. Effect of praziquantel on protozoan parasites. Lancet 345 (8945), 316–317.

FAO (Food and Agriculture Organization of the United Nations), 2020. The State of World Fisheries and Aquaculture 2020 - Sustainability in Action. FAO, Rome. http://www.fao.org/state-of-fisheries-aquaculture/en/. (Accessed 21 January 2021).

Foreyt, W.J., Gorham, J.R., 1988. Preliminary evaluation of praziquantel against metacercariae of *Nanophyetus salmincola* in Chinook Salmon (*Oncorhynchus tshawytscha*). J. Wildl. Dis. 24 (3), 551–554.

Forwood, J.M., Bubner, E.J., Landos, M., D'Antignana, T., Deveney, M.R., 2016a. Praziquantel treatment for yellowtail kingfish (*Seriola lalandi*): dose and duration safety study. Fish Physiol. Biochem. 42 (1), 103–109.

Forwood, J.M., Bubner, E.J., Landos, M., Deveney, M.R., D'Antignana, T., 2016b. Praziquantel delivery via moist pellets to treat monogenean parasites of yellowtail kingfish *Seriola lalandi*: efficacy and feed acceptance. Dis. Aquat. Org. 121 (3), 201–209.

Forwood, J.M., Harris, J.O., Deveney, M.R., 2013a. Efficacy of bath and orally administered praziquantel and fenbendazole against *Lepidotrema bidyana* Murray, a monogenean parasite of silver perch, *Bidyanus bidyanus* (Mitchell). J. Fish. Dis. 36 (11), 939–947.

Forwood, J.M., Harris, J.O., Deveney, M.R., 2013b. Efficacy of current and alternative bath treatments for *Lepidotrema bidyana* infecting silver perch. Bidyanus bidyanus. Aquaculture 416–417, 65–71.

Fridman, S., Sinai, T., Zilberg, D., 2014. Efficacy of garlic based treatments against monogenean parasites infecting the guppy (*Poecilia reticulata* (Peters)). Vet. Parasitol. 203 (1–2), 51–58.

Frohberg, H., 1984. Results of toxicological studies on praziquantel. Arzneimittelforschung 34 (9B), 1137–1144.

FHF (The Norwegian Fishery and Aquaculture Industry Research Fund), 2006. *Bendelorm (Eubothrium sp.) hos laks (Salmo salar): Utprøving av nye behandlingsmidler og utvikling av et in vitro bioassay for måling av resistens overfor praziquantel - Rapport fra et pilotprosjekt* [Tapeworm (*Eubothrium* sp.) in salmon (*Salmo salar*): trial of new therapeutics and development of an *in vitro* bioassay to measure praziquantel resistance - Report] [in Norwegian]. https://www.fhf.no/prosjekter/prosjektbasen/551024/. (Accessed 25 April 2020).

FHF (The Norwegian Fishery and Aquaculture Industry Research Fund) (2008). reportResistens hos bendelorm (Eubothrium sp.) Sluttrapport 2008 [Resistance in tapeworm (Eubothrium sp.) Final Report 2008]. https://www.fhf.no/prosjekter/prosjektbasen/552024/(accessed 25 April 2020) [in Norwegian].

Gallego, L., Gracenea, M., 2015. Praziquantel efficacy against *Brachylaima* sp. metacercariae (Trematoda: Brachylaimidae) parasitizing the edible landsnail *Cornu aspersum* and its HPLC-MS/MS residue determination. Exp. Parasitol. 157, 92–102.

Goodenough, A.E., Webb, J.C., Yardley, J., 2019. Environmentally-realistic concentrations of anthelmintic drugs affect survival and motility in the cosmopolitan earthworm *Lumbricus terrestris* (Linnaeus, 1758). Appl. Soil Ecol. 137, 87–95.

Goto, K., 2019. Solid Oral Agents for Administering to Fishes, Feed for Fish Breeding Containing Agents Concerned, and Methods of Administering Agents to Fish. JP6472341B2.

Grant, A.N., 2002. Medicines for sea lice. Pest Manag. Sci. 58 (6), 521–527.

Grau, A., Crespo, S., Pastor, E., Gonzalez, P., Carbonell, E., 2003. High infection by *Zeuxapta seriolae* (Monogenea: Heteraxinidae) associated with mass mortalities of amberjack *Seriola dumerili* Risso reared in sea cages in the Balearic Islands (western Mediterranean). Bull. Eur. Assoc. Fish Pathol. 23 (3), 139–142.

Greenberg, R.M., Doenhoff, M.J., 2017. Chemotherapy and drug resistance in schistosomiasis and other trematode and cestode infections. In: Mayers, D.L., Sobel, J.D., Ouellette, M., Kaye, K.S., Marchaim, D. (Eds.), Antimicrobial Drug Resistance: Mechanisms of Drug Resistance, vol. 1. Springer, Cham, pp. 705–734.

Hadfield, C.A., Clayton, L.A., 2011. Fish quarantine: current practices in public zoos and aquaria. J. Zoo Wildl. Med. 42 (4), 641–650.

Hardy-Smith, P., Ellis, D., Humphrey, J., Evans, M., Evans, D., Rough, K., Valdenegro, V., Nowak, B., 2012. *In vitro* and *in vivo* efficacy of anthelmintic compounds against blood fluke (*Cardicola forsteri*). Aquaculture 334–337, 39–44.

Harnett, W., 1988. The anthelmintic action of praziquantel. Parasitol. Today 4 (5), 144–146.

Hashem, H., Ibrahim, A.E., Elhenawee, M., 2017. A rapid stability indicating LC-method for determination of praziquantel in presence of its pharmacopoeial impurities. Arab. J. Chem. 10, S35–S41.

Havlíková, L., Šatínský, D., Solich, P., 2016. Aspects of decontamination of ivermectin and praziquantel from environmental waters using advanced oxidation technology. Chemosphere 144, 21–28.

Hempel, H., Scheffczyk, A., Schallnass, H.J., Lumaret, J.P., Alvinerie, M., Rombke, J., 2006. Toxicity of four veterinary parasiticides on larvae of the dung beetle Aphodius constans in the laboratory. Environ. Toxicol. Chem. 25 (12), 3155–3163.

Hirazawa, N., Akiyama, K., Umeda, N., 2013. Differences in sensitivity to the anthelmintic praziquantel by the skin-parasitic monogeneans *Benedenia seriolae* and *Neobenedenia girellae*. Aquaculture 404–405, 59–64.

Hirazawa, N., Mitsuboshi, T., Hirata, T., Shirasu, K., 2004. Susceptibility of spotted halibut *Verasper variegatus* (Pleuronectidae) to infection by the monogenean *Neobenedenia girellae* (Capsalidae) and oral therapy trials using praziquantel. Aquaculture 238 (1–4), 83–95.

Hirazawa, N., Ohtaka, T., Hata, K., 2000. Challenge trials on the anthelmintic effect of drugs and natural agents against the monogenean *Heterobothrium okamotoi* in the tiger puffer *Takifugu rubripes*. Aquaculture 188, 1–13.

Hoai, T.D., 2019. Reproductive strategies of parasitic flatworms (Platyhelminthes, Monogenea): the impact on parasite management in aquaculture. Aquacult. Int. 28 (1), 421–447.

Hoai, T.D., Van, K.V., 2014. Efficacy of praziquantel against external parasites infecting freshwater fish. J Sci & Devel 12 (5), 711–719.

Hodgkinson, J.E., Kaplan, R.M., Kenyon, F., Morgan, E.R., Park, A.W., Paterson, S., Babayan, S.A., Beesley, N.J., Britton, C., Chaudhry, U., Doyle, S.R., 2019. Refugia and anthelmintic resistance: concepts and challenges. Int. J. Parasitol. Drugs Drug. Resist. 10, 51–57.

Hormazábal, V., Yndestad, M., 1995. Determination of praziquantel in medicated fish feed and sediment by HPLC. J. Liq. Chromatogr. 18 (6), 1231–1238.

Huston, D.C., Ogawa, K., Shirakashi, S., Nowak, B.F., 2020. Metazoan parasite life cycles: significance for fish mariculture. Trends Parasitol. 36 (12), 1002–1012.

Hutson, K.S., Ernst, I., Whittington, I.D., 2007. Risk assessment for metazoan parasites of yellowtail kingfish *Seriola lalandi* (Perciformes: Carangidae) in South Australian sea-cage aquaculture. Aquaculture 271 (1), 85–99.

Ido, A., Kanemaru, M., Tanioka, Y., 2019. Preliminary monitoring of praziquantel in water and sediments at a Japanese amberjack (*Seriola quinqueradiata*) Aquaculture Site. Fishes 4 (2), 24.

Iles, A.C., Archdeacon, T.P., Bonar, S.A., 2012. Novel praziquantel treatment regime for controlling Asian tapeworm infections in pond-reared fish. N. Am. J. Aquacult. 74 (1), 113–117.

Ishimaru, K., Mine, R., Shirakashi, S., Kaneko, E., Kubono, K., Okada, T., Sawada, Y., Ogawa, K., 2013. Praziquantel treatment against *Cardicola* blood flukes: determination of the minimal effective dose and pharmacokinetics in juvenile Pacific bluefin tuna. Aquaculture 402, 24–27.

Janse, M., Borgsteede, F.H.M., 2003. Praziquantel treatment of captive whitespotted eagle rays (*Aetobatus narinari*) infested with monogean trematodes. Bull. Eur. Assoc. Fish Pathol. 23 (4), 152–156.

Jesudoss Chelladurai, J., Kifleyohannes, T., Scott, J., Brewer, M.T., 2018. Praziquantel resistance in the zoonotic cestode *Dipylidium caninum*. Am. J. Trop. Med. Hyg. 99 (5), 1201–1205.

Jones, M., 2004. Cultured aquatic species information programme. Salmo salar. online. In: FAO Fisheries and Aquaculture Department. Rome. Updated 1 January 2004. http://www.fao.org/fishery/culturedspecies/Salmo_salar/en. (Accessed 5 April 2020).

Joubert, C.J.H., 2012. The Potential of Commercial Praziquantel Formulations as" off Label" Treatments for *Diplectanum Oliveri* (Monogenea) Infecting Cultured argyrosomus Species in the South African Marine Finfish Aquaculture Industry. Masters thesis. University of the Western Cape.

Jung, H., Medina, R., Castro, N., Corona, T., Sotelo, J., 1997. Pharmacokinetic study of praziquantel administered alone and in combination with cimetidine in a single-day therapeutic regimen. Antimicrob. Agents Chemother. 41 (6), 1256–1259.

Keiser, J., Utzinger, J., 2004. Chemotherapy for major food-borne trematodes: a review. Expet Opin. Pharmacother. 5 (8), 1711–1726.

Kim, C.S., Cho, J.B., Ahn, K.J., Lee, J.I., Kim, K.H., 2003. Depletion of praziquantel in muscle tissue and skin of cultured rockfish (*Sebastes schlegeli*) under the commercial culture conditions. Aquaculture 219 (1–4), 1–7.

Kim, K.H., Cho, J.B., 2000. Treatment of *Microcotyle sebastis* (Monogenea: polyopisthocotylea) infestation with praziquantel in an experimental cage simulating commercial rockfish *Sebastes schlegeli* culture conditions. Dis. Aquat. Org. 40 (3), 229–231.

Kim, K.H., Kim, C.S., 2002. Cimetidine enhances the plasma praziquantel concentration and treatment efficacy against *Microcotyle sebastis* in cultured rockfish *Sebastes schlegeli*. Dis. Aquat. Org. 49 (1), 45–49.

Kim, K.H., Kim, C.S., Kim, J.W., 2001a. Depletion of praziquantel in plasma and muscle tissue of cultured rockfish *Sebastes schlegeli* after oral and bath treatment. Dis. Aquat. Org. 45 (3), 203–207.

Kim, K.H., Lee, E.H., Kwon, S.R., Cho, J.B., 2001b. Treatment of *Microcotyle sebastis* infestation in cultured rockfish *Sebastes schlegeli* by oral administration of praziquantel in combination with cimetidine. Dis. Aquat. Org. 44 (2), 133–136.

Kim, K.H., Park, S.I., Jee, B.Y., 1998. Efficacy of oral administration of praziquantel and mebendazole against Microcotyle sebastis (Monogenea) infestation of cultured rockfish (*Sebastes schlegeli*). Fish Pathol. 33 (5), 467–471.

Kline, S.J., Archdeacon, T.P., Bonar, S.A., 2009. Effects of praziquantel on eggs of the Asian tapeworm *Bothriocephalus acheilognathi*. N. Am. J. Aquacult. 71 (4), 380–383.

Kobayashi, M., Msangi, S., Batka, M., Vannuccini, S., Dey, M.M., Anderson, J.L., 2015. Fish to 2030: the role and opportunity for aquaculture. Aquacult. Econ. Manag. 19 (3), 282–300.

Kogiannou, D., Nikoloudaki, C., Rigos, G., 2021. Absorption and depletion of dietary administered praziquantel in greater amberjack, *Seriola dumerili*. Aquaculture 535, 736354.

Kogiannou, D., Rigos, G., 2021. Praziquantel depletion from muscle plus skin tissue of gilthead sea bream (*Sparus aurata*). Mediterr. Mar. Sci. 22 (1), 121–124.

Kolasa, J., 2000. The biology and ecology of lotic microturbellarians. Freshw. Biol. 44 (1), 5–14.

Kramers, P.G.N., Gentile, J.M., Gryseels, B.J.A.M., Jordan, P., Katz, N., Mott, K.E., Mulvihill, J.J., Seed, J.L., Frohberg, H., 1991. Review of the genotoxicity and carcinogenicity of antischistosomal drugs; is there a case for a study of mutation epidemiology? Report of a task group on mutagenic antischistosomals. Mutat. Res. Rev. Genet. Toxicol. 257 (1), 49–89.

Lafferty, K.D., Harvell, C.D., Conrad, J.M., Friedman, C.S., Kent, M.L., Kuris, A.M., Powell, E.N., Rondeau, D., Saksida, S.M., 2015. Infectious diseases affect marine fisheries and aquaculture economics. Ann. Rev. Mar. Sci 7, 471–496.

Landa, P., Prerostova, S., Langhansova, L., Marsik, P., Vankova, R., Vanek, T., 2018. Transcriptomic response of *Arabidopsis thaliana* roots to naproxen and praziquantel. Ecotoxicol. Environ. Saf. 166, 301–310.

Lateef, M., Zargar, S.A., Khan, A.R., Nazir, M., Shoukat, A., 2008. Successful treatment of niclosamide-and praziquantel-resistant beef tapeworm infection with nitazoxanide. Int. J. Infect. Dis. 12 (1), 80–82.

Levsen, A., Lunestad, B.T., Berland, B., 2008. Parasites in farmed fish and fishery products. In: Lie, Ø. (Ed.), Improving Farmed Fish Quality and Safety. Woodhead Publishing, Oxford, pp. 428–445.

Levy, G., Zilberg, D., Paladini, G., Fridman, S., 2015. Efficacy of ginger-based treatments against infection with *Gyrodactylus turnbulli* in the guppy (*Poecilia reticulata* (Peters)). Vet. Parasitol. 209 (3–4), 235–241.

Lewbart, G.A., Gratzek, J.B., 1990. The use of praziquantel in the elimination of intestinal cestodes from the red snakehead (*Channa micropletes*). Proc Int Assoc Aquat Animal Med 21, 11–13.

Lia, R., Zizzo, N., Tinelli, A., Lionetti, A., Cantacessi, C., Otranto, D., 2007. Mass mortality in wild greater amberjack (*Seriola dumerili*) infected by *Zeuxapta seriolae* (Monogenea: Heteraxinidae) in the Jonian Sea. Bull. Eur. Assoc. Fish Pathol. 27 (3), 108.

Lima dos Santos, C.A.M., Howgate, P., 2011. Fishborne zoonotic parasites and aquaculture: a review. Aquaculture 318 (3), 253–261.

Lorio, W.J., 1989. Experimental control of metacercariae of the yellow grub *Clinostomum marginatum* in channel catfish. J. Aquat. Anim. Health 1 (4), 269–271.

Lunestad, B.T., Hannisdal, R., Samuelsen, O., 2015. Safety of medical feed additives in the food chain. In: Davis, D.A. (Ed.), Feed and Feeding Practices in Aquaculture. Woodhead Publishing, Oxford, pp. 251–268.

Manenti, R., Bianchi, B., 2014. Distribution of the triclad *Polycelis felina* (Planariidae) in Aezkoa Mountains: effect of stream biotic features. Acta Zool. Bulg. 66, 271–275.

Mansell, B., Powell, M.D., Ernst, I., Nowak, B.F., 2005. Effects of the gill monogenean *Zeuxapta seriolae* (Meserve, 1938) and treatment with hydrogen peroxide on pathophysiology of kingfish, *Seriola lalandi* Valenciennes, 1833. J. Fish. Dis. 28 (5), 253–262.

Marsik, P., Podlipna, R., Vanek, T., 2017. Study of praziquantel phytoremediation and transformation and its removal in constructed wetland. J. Hazard Mater. 323, 394–399.

Martens, P.M., Schockaert, E.R., 1986. The importance of turbellarians in the marine meiobenthos: a review. Hydrobiologia 132 (1), 295–303.

McCarthy, I., Carter, C., Houlihan, D., 1992. The effect of feeding hierarchy on individual variability in daily feeding of rainbow trout, *Oncorhynchus mykiss* (Walbaum). J. Fish. Biol. 41 (2), 257–263.

Metcalfe, C., Boxall, A., Fenner, K., Kolpin, D.W., Silberhorn, E., Staveley, J., 2008. Exposure assessment of veterinary medicines in aquatic systems. In: Crane, M., Boxall, A.B.A., Barrett, K. (Eds.), Veterinary Medicines in the Environment. CRC Press, Boca Raton, pp. 57–96.

Mitchell, A., Darwish, A., 2009. Efficacy of 6-, 12-, and 24-h praziquantel bath treatments against Asian tapeworms *Bothriocephalus acheilognathi* in grass carp. N. Am. J. Aquacult. 71 (1), 30–34.

Mitchell, A.J., 1995. Importance of treatment duration for praziquantel used against larval digenetic trematodes in sunshine bass. J. Aquat. Anim. Health 7 (4), 327–330.

Mitchell, A.J., 2004. Effectiveness of praziquantel bath treatments against *Bothriocephalus acheilognathi* in grass carp. J. Aquat. Anim. Health 16 (3), 130–136.

Mitchell, A.J., Hobbs, M.S., 2007. The acute toxicity of praziquantel to grass carp and golden shiners. N. Am. J. Aquacult. 69 (3), 203–206.

Mitchell, C., 1993. Eubothrium. Aquaculture Information Series, No 14. Scottish Office Agriculture and Fisheries Department, 8pp.

Mohammad, K.A., 1998. Effectiveness of praziquantel in treatment of intestinal amoebiasis and giardiasis. East. Mediterr. Health J. 4 (1), 161–163.

Morales-Serna, F.N., Chapa-Lopez, M., Martinez-Brown, J.M., Ibarra-Castro, L., Medina-Guerrero, R.M., Fajer-Avila, E.J., 2018. Efficacy of praziquantel and a combination anthelmintic (Adecto®) in bath treatments against *Tagia ecuadori* and *Neobenedenia melleni* (Monogenea), parasites of bullseye puffer fish. Aquaculture 492, 361–368.

Morley, N.J., 2009. Environmental risk and toxicology of human and veterinary waste pharmaceutical exposure to wild aquatic host–parasite relationships. Environ. Toxicol. Pharmacol. 27 (2), 161–175.

Moser, M., Sakanari, J., Heckmann, R., 1986. The effects of praziquantel on various larval and adult parasites from freshwater and marine snails and fish. J. Parasitol. 72 (1), 175–176.

NIPH (National Institute of Public Health), 2016. *Legemidler I Fiskeoppdrett 2016* [Medicines in Fish Farming 2016] [in Norwegian]. https://www.fhi.no/hn/legemiddelbruk/fisk/2016-salg-av-lakselusmidler-er-synkende/. (Accessed 12 April 2020).

Nagano, T., Isshiki, T., Sakamoto, H., 2013. Fish Disease Control Experiments 2-3, H13. Bull Kagawa Pref Fish Exp Stn, pp. 97–99 ([in Japanese]).

Neumann, L., Bridle, A., Leef, M., Nowak, B., 2018. Annual variability of infection with *Cardicola forsteri* and *Cardicola orientalis* in ranched and wild southern bluefin tuna (*Thunnus maccoyii*). Aquaculture 487, 1–6.

Noga, E.J., 2010. Fish Disease: Diagnosis and Treatment. John Wiley & Sons, 536pp.

Nogi, T., Zhang, D., Chan, J.D., Marchant, J.S., 2009. A novel biological activity of praziquantel requiring voltage-operated Ca2+ channel beta subunits: subversion of flatworm regenerative polarity. PLoS Neglected Trop. Dis. 3 (6), e464.

Nowak, B.F., 2004. Assessment of health risks to southern bluefin tuna under current culture conditions. Bull. Eur. Assoc. Fish Pathol. 24 (1), 45–51.

Nwani, C.D., Nnaji, M.C., Oluah, S.N., Echi, P.C., Nwamba, H.O., Ikwuagwu, O.E., Ajima, M.N., 2014. Mutagenic and physiological responses in the juveniles of African catfish, *Clarias gariepinus* (Burchell 1822) following short term exposure to praziquantel. Tissue Cell 46 (4), 264–273.

O'Brien, N.Y., 2012. 'Evidence-based Veterinary Medicine in Finfish Aquaculture in Newfoundland and Labrador'. PhD thesis. University of Prince Edward Island.

Obiekezie, A., Okafor, N., 1995. Toxicity of four commonly used chemotherapeutic compounds to fry of the African catfish, *Clarias gariepinus* (Burchell). Aquacult. Res. 26 (6), 441–445.

Ogawa, K., 2015. Diseases of cultured marine fishes caused by Platyhelminthes (Monogenea, Digenea, Cestoda). Parasitology 142 (1), 178–195.

Okabe, K., 2000. Hada-clean, an antiparasitic drug for oral treatment of fish parasites. Doyaku Kenkyu 60, 1–12.

Onaka, E., Martins, M., Moraes, F., 2003. Albendazole and praziquantel efficacy against *Anacanthorus penilabiatus* (monogenea: dactylogyridae), gill parasite of *Piaractus mesopotamicus* (osteichthyes: characidae). I. Therapeutic baths. Bol. Inst. Pesca. 29 (2), 101–107.

Park, S.K., Friedrich, L., Yahya, N.A., Rohr, C.M., Chulkov, E.G., Maillard, D., Rippmann, F., Spangenberg, T., Marchant, J.S., 2021. Mechanism of praziquantel action at a parasitic flatworm ion channel. Sci. Transl. Med. 13 (625), eabj5832.
Park, S.K., Gunaratne, G.S., Chulkov, E.G., Moehring, F., McCusker, P., Dosa, P.I., Chan, J.D., Stucky, C.L., Marchant, J.S., 2019. The anthelmintic drug praziquantel activates a schistosome transient receptor potential channel. J. Biol. Chem. 294 (49), 18873–18880.
Park, S.K., Marchant, J.S., 2020. The journey to discovering a flatworm target of praziquantel: a long TRP. Trends Parasitol. 36 (2), 182–194.
Partridge, G.J., Burge, T., Lymbery, A.J., 2017. A comparison of the palatability of racemic praziquantel and its two enantioseparated isomers in yellowtail kingfish *Seriola lalandi* (Valenciennes, 1833). Aquacult. Res. 48 (4), 1735–1743.
Partridge, G.J., Michael, R.J., Thuillier, L., 2014. Praziquantel form, dietary application method and dietary inclusion level affect palatability and efficacy against monogenean parasites in yellowtail kingfish. Dis. Aquat. Org. 109 (2), 155–163.
Partridge, G.J., Rao, S., Woolley, L.D., Pilmer, L., Lymbery, A.J., Prestidge, C.A., 2019. Bioavailability and palatability of praziquantel incorporated into solid-lipid nanoparticles fed to yellowtail kingfish *Seriola lalandi*. Comp. Biochem. Physiol. C Toxicol. Pharmacol. 218, 14–20.
Periša, M., Babić, S., 2014. Simultaneous determination of pharmaceuticals and some of their metabolites in wastewaters by high performance liquid chromatography with tandem mass spectrometry. J. Separ. Sci. 37 (11), 1289–1296.
Patrick, D.M., Isaac-Renton, J., 1992. Praziquantel failure in the treatment of *Fasciola hepatica*. Can. J. Infect Dis. 3 (1), 33–36.
Pilmer, L., 2016. 'Novel Methods of Improving the Palatability of Feeds Containing Praziquantel for Commercially Cultured Yellowtail Kingfish'. Honours thesis. Murdoch University.
Plumb, J.A., Rogers, W.A., 1990. Effect of Droncit (praziquantel) on yellow grubs *Clinostomum marginatum* and eye flukes *Diplostomum spathaceum* in channel catfish. J. Aquat. Anim. Health 2 (3), 204–206.
Polderman, A., Gryseels, B., Gerold, J., Mpamila, K., Manshande, J., 1984. Side effects of praziquantel in the treatment of *Schistosoma mansoni* in Maniema, Zaire. Trans. R. Soc. Trop. Med. Hyg. 78 (6), 752–754.
Polinski, M., Hamilton, D.B., Nowak, B., Bridle, A., 2013. SYBR, TaqMan, or both: highly sensitive, non-invasive detection of *Cardicola* blood fluke species in Southern Bluefin Tuna (*Thunnus maccoyii*). Mol. Biochem. Parasitol. 191 (1), 7–15.
Pool, D., Ryder, K., Andrews, C., 1984. The control of *Bothriocephalus acheilognathi* in grass carp. Aquacult. Res. 15 (1), 31–33.
Power, C., Webber, C., Rough, K., Staunton, R., Nowak, B.F., Bott, N.J., 2019. The effect of different treatment strategies on *Cardicola* spp. (Trematoda: Aporocotylidae) infection in ranched southern bluefin tuna (*Thunnus maccoyii*) from Port Lincoln, South Australia. Aquaculture 513, 734401.
Power, C., Nowak, B.F., Cribb, T.H., Bott, N.J., 2020. Bloody flukes: a review of aporocotylids as parasites of cultured marine fishes. Int. J. Parasitol. 50 (10–11), 743–753.
Poynton, S.L., Campbell, T.W., Palm, H.W., 1997. Skin lesions in captive lemon sharks *Negaprion brevirostris* (Carcharhinidae) associated with the monogenean *Neodermophthirius harkemai* Price, 1963 (Microbothriidae). Dis. Aquat. Org. 31, 29–33.
Reed, P., Francis-Floyd, R., Klinger, R. & Petty, D. (2019). Monogenean parasites of fish. Fisheries and aquatic sciences, IFAS Extension, University of Florida. FA28. https://edis.ifas.ufl.edu (accessed 21 April 2020).
Rigos, G., Kogiannou, D., Vasilaki, A., Kotsiri, M., 2021. Evaluation of praziquantel efficacy against *Zeuxapta seriolae* infections in greater amberjack, *Seriola dumerili*. Appl. Sci. 11, 4656.
Ruppert, E.E., Barnes, R.D., Barnes, R.D., 1994. Invertebrate Zoology, sixth ed. Saunders College Publishing, Fort Worth.
Saksvik, M., Nilsen, F., Nylund, A., Berland, B., 2001a. Effect of marine *Eubothrium* sp. (Cestoda: pseudophyllidea) on the growth of Atlantic salmon, *Salmo salar* L. J. Fish. Dis. 24 (2), 111–119.
Saksvik, M., Nylund, A., Nilsen, F., Hodneland, K., 2001b. Experimental infection of Atlantic salmon (*Salmo salar*) with marine *Eubothrium* sp.(Cestoda: pseudophyllidea): observations on the life cycle, aspects of development and growth of the parasite. Folia Parasitol. 48 (2), 118–126.
Sanmartín Durán, M.L., Caamaño-García, F., Fernández casal, J., Leiro, J., Ubeira, F.M., 1989. Anthelminthic activity of praziquantel, niclosamide, netobimin and mebendazole against Bothriocephalus scorpii naturally infecting turbot (Scophthalmus maximus). Aquaculture 76, 199–201.
Santamarina, M.T., Tojo, J., Ubeira, F.M., Quinteiro, P., Sanmartin, M.L., 1991. Anthelmintic treatment against *Gyrodactylus* sp. infecting rainbow trout *Oncorhynchus mykiss*. Dis. Aquat. Org. 10, 39–43.
Scala, A., Urrai, G., Varcasia, A., Nicolussi, P., Mulas, M., Goddi, L., Pipia, A.P., Sanna, G., Genchi, M., Bandino, E., 2016. Acute visceral cysticercosis by Taenia hydatigena in lambs and treatment with praziquantel. J. Helminthol. 90 (1), 113–116.
Schalch, S.H., de Moraes, F.R., Soares, V.E., 2009. [Praziquantel, levamisole and diflubenzuron in the control of dolops carvalhoi (Crustacea: Branchiura) and Anacanthorus penilabiatus (monogenea: dactylogyridae) in piaractus mesopotamicus Holmberg, 1887 (osteichthyes: characidae)]. Rev. Bras. Parasitol. Vet. 18 (1), 53–59.
Schmahl, G., Mehlhorn, H., 1985. Treatment of fish parasites. 1. Praziquantel effective against Monogenea (*Dactylogyrus vastator, Dactylogyrus extensus, Diplozoon paradoxum*). Z. Parasitenkd. 71 (6), 727–737.
Schmahl, G., Taraschewski, H., 1987. Treatment of fish parasites. 2. Effects of praziquantel, niclosamide, levamisole-HCl, and metrifonate on monogenea (*Gyrodactylus aculeati, Diplozoon paradoxum*). Parasitol. Res. 73 (4), 341–351.
Sharp, N.J., Diggles, B.K., Poortenaar, C.W., Willis, T.J., 2004. Efficacy of Aqui-S, formalin and praziquantel against the monogeneans, *Benedenia seriolae* and *Zeuxapta seriolae*, infecting yellowtail kingfish *Seriola lalandi lalandi* in New Zealand. Aquaculture 236 (1–4), 67–83.
Shirakashi, S., Andrews, M., Kishimoto, Y., Ishimaru, K., Okada, T., Sawada, Y., Ogawa, K., 2012a. Oral treatment of praziquantel as an effective control measure against blood fluke infection in Pacific bluefin tuna (*Thunnus orientalis*). Aquaculture 326–329, 15–19.
Shirakashi, S., Kishimoto, Y., Kinami, R., Katano, H., Ishimaru, K., Murata, O., Itoh, N., Ogawa, K., 2012b. Morphology and distribution of blood fluke eggs and associated pathology in the gills of cultured Pacific bluefin tuna, *Thunnus orientalis*. Parastol Int 61 (2), 242–249.
Shirakashi, S., Ogawa, K., 2016. Blood fluke infections in marine cultured fish. Fish Pathol. 51 (3), 92–98.
Sitjà-Bobadilla, A., de Felipe, M.C., Alvarez-Pellitero, P., 2006. *In vivo* and *in vitro* treatments against *Sparicotyle chrysophrii* (Monogenea: microcotylidae) parasitizing the gills of gilthead sea bream (*Sparus aurata* L.). Aquaculture 261 (3), 856–864.
Smith, M., Warmolts, D., Thoney, D., Hueter, R., Murray, M., Ezcurra, J. (Eds.), 2017. The Elasmobranch Husbandry Manual II: Recent Advances in the Care of Sharks, Rays and Their Relatives. Ohio Biological Survey, Ohio.
Stelma, F., Talla, I., Sow, S., Kongs, A., Niang, M., Polman, K., Deelder, A.M., Gryseels, B., 1995. Efficacy and side effects of praziquantel in an epidemic focus of Schistosoma mansoni. Am. J. Trop. Med. Hyg. 53 (2), 167–170.
Stephens, F.J., Cleary, J.J., Jenkins, G., Jones, J.B., Raidal, S.R., Thomas, J.B., 2003. Treatments to control *Haliotrema abaddon* in the West Australian dhufish, *Glaucosoma hebraicum*. Aquaculture 215 (1–4), 1–10.
Stetter, M.D., Davis, J., Capobianco, J., Coston, C., 1999. Use of praziquantel for the control of monogenetic trematodes in public marine aquariums. Proc. Int. Assn. Aquat. Anim. Med. 30, 85–86.
Sudová, E., Piačková, V., Kroupová, H., Pijáček, M., Svobodová, Z., 2009. The effect of praziquantel applied per os on selected haematological and biochemical indices in common carp (*Cyprinus carpio* L.). Fish Physiol. Biochem. 35 (4), 599–605.
Sudová, E., Piačková, V., Velíšek, J., Pijáček, M., Svobodová, Z., 2010. Efficacy testing of orally administered praziquantel to common carp naturally infected by Caryophyllidean tapeworms (Platyhelminthes: eucestoda). Acta Vet. 79 (9), S73–S78.
Székely, C., Molnár, K., 1990. Treatment of *Ancylodiscoides vistulensis* monogenean infestation of the European catfish (*Silurus glanis*). Bull. Eur. Assoc. Fish Pathol. 10 (3), 74–77.
Székely, C., Molnár, K., 1991. Praziquantel (Droncit) is effective against diplostomosis of grasscarp *Ctenopharyngodon idella* and silver carp *Hypophthalmichthys molitrix*. Dis. Aquat. Org. 11 (2), 147–150.
Thomas, A., Dawson, M.R., Ellis, H., Stamper, M.A., 2016. Praziquantel degradation in marine aquarium water. PeerJ 4, e1857.
Thomas, C.M., Timson, D.J., 2018. The mechanism of action of praziquantel: six hypotheses. Curr. Top. Med. Chem. 18 (18), 1575–1584.
Thomas, C.M., Timson, D.J., 2020. The mechanism of action of praziquantel: can new drugs exploit similar mechanisms? Curr. Med. Chem. 27 (5), 676–696.
Thoney, D.A., 1990. The effects of trichlorfon, praziquantel and copper sulphate on various stages of the monogenean *Benedeniella posterocolpa*, a skin parasite of the cownose ray, *Rhinoptera bonasus* (Mitchill). J. Fish. Dis. 13 (5), 385–389.
Thoney, D.A., Hargis, W.J., 1991. Monogenea (platyhelminthes) as hazards for fish in confinement. Annu. Rev. Fish Dis. 1, 133–153.
Tinga, N., De, N., Vien, H.V., Chau, L., Toan, N.D., Kager, P.A., Vries, P.J., 1999. Little effect of praziquantel or artemisinin on clonorchiasis in Northern Vietnam. A pilot study. Trop. Med. Int. Health 4 (12), 814–818.
Tojo, J.L., Santamarina, M.T., 1998. Oral pharmacological treatments for parasitic diseases of rainbow trout *Oncorhynchus mykiss*. II. *Gyrodactylus* sp. Dis. Aquat. Org. 33 (3), 187–193.
Tubbs, L.A., Tingle, M.D., 2006a. Bioavailability and pharmacokinetics of a praziquantel bolus in kingfish *Seriola lalandi*. Dis. Aquat. Org. 69 (2–3), 233–238.
Tubbs, L.A., Tingle, M.D., 2006b. Effect of dose escalation on multiple dose pharmacokinetics of orally administered praziquantel in kingfish *Seriola lalandi*. Aquaculture 261 (4), 1168–1174.
van Wyk, J.A., 2001. Refugia—overlooked as perhaps the most potent factor concerning the development of anthelmintic resistance. Onderstepoort J. Vet. Res. 68 (1), 55–67.
Vaughan, D.B., Chisholm, L.A., 2010. *Heterocotyle tokoloshei* sp. nov. (Monogenea, monocotylidae) from the gills of *Dasyatis brevicaudata* (dasyatidae) kept in captivity at two oceans aquarium, Cape town, South Africa: description and notes on treatment. Acta Parasitol. 55 (2), 108–114.
Vickerman, K., 1992. The diversity and ecological significance of Protozoa. Biodivers. Conserv. 1 (4), 334–341.
Voutilainen, A., Saarinen, M., Suonpaa, A., Taskinen, J., 2009. *In vitro* efficacy of praziquantel against the cercariae of *Diplostomum* sp., *Rhipidocotyle fennica* and *R. campanula*. J. Fish. Dis. 32 (10), 907–909.
Ward, D.L., 2007. Removal and quantification of Asian tapeworm from bonytail chub using praziquantel. N. Am. J. Aquacult. 69 (3), 207–210.
Webster, B.L., Diaw, O.T., Seye, M.M., Faye, D.S., Stothard, J.R., Sousa-Figueiredo, J.C., Rollinson, D., 2013. Praziquantel treatment of school children from single and mixed infection foci of intestinal and urogenital schistosomiasis along the Senegal River Basin: monitoring treatment success and re-infection patterns. Acta Trop. 128 (2), 292–302.
Wegner, D., 1984. The profile of the trematodicidal compound praziquantel. Arzneim. Forsch. 34 (9B), 1132–1136.

Whittington, I.D., Ernst, I., 2002. Migration, site-specificity and development of *Benedenia lutjani* (monogenea: Capsalidae) on the surface of its host, *Lutjanus carponotatus* (pisces: lutjanidae). Parasitology 124 (4), 423–434.
Whittington, I.D., 2012. *Benedenia seriolae* and *Neobenedenia* species. In: Woo, P.T.K., Buchmann, K. (Eds.), Fish Parasites: Pathobiology and Protection. CABI, Wallingford, pp. 225–244.
Williams, R.E., 2009. 'Oral Treatments for Monogenean Parasities of Farmed Yellowtails, *Seriola* Spp. (Carangidae)'. PhD thesis. University of Adelaide.
Williams, R.E., Ernst, I., Chambers, C.B., Whittington, I.D., 2007. Efficacy of orally administered praziquantel against *Zeuxapta seriolae* and *Benedenia seriolae* (Monogenea) in yellowtail kingfish *Seriola lalandi*. Dis. Aquat. Org. 77 (3), 199–205.
Woo, P.T.K., Buchmann, K. (Eds.), 2012. Fish Parasites: Pathobiology and Protection. CABI, Wallingford.
WHO (World Health Organization), Stuart, M.C., Kouimtzi, M., Hill, S.R., 2009. WHO Model Formulary 2008. World Health Organization, Geneva. https://apps.who.int/iris/handle/10665/44053. (Accessed 21 April 2020).
Xiao, S.-h., Catto, B.A., Webster Jr., L.T., 1985. Effects of praziquantel on different developmental stages of *Schistosoma mansoni in vitro* and *in vivo*. J. Infect. Dis. 151 (6), 1130–1137.
Xie, X., Zhao, Y., Yang, X., Hu, K., 2015. Comparison of praziquantel pharmacokinetics and tissue distribution in fresh and brackish water cultured grass carp (*Ctenopharyngodon idellus*) after oral administration of single bolus. BMC Vet. Res. 11, 84.
Yamamoto, S., Shirakashi, S., Morimoto, S., Ishimaru, K., Murata, O., 2011. Efficacy of oral praziquantel treatment against the skin fluke infection of cultured chub mackerel, *Scomber japonicus*. Aquaculture 319 (1–2), 53–57.
Zhang, C., Ling, F., Chi, C., Wang, G.X., 2013. Effects of praziquantel and sanguinarine on expression of immune genes and susceptibility to *Aeromonas hydrophila* in goldfish (*Carassius auratus*) infected with *Dactylogyrus intermedius*. Fish Shellfish Immunol. 35 (4), 1301–1308.
Zhang, X.P., Li, W.X., Ai, T.S., Zou, H., Wu, S.G., Wang, G.T., 2014. The efficacy of four common anthelmintic drugs and traditional Chinese medicinal plant extracts to control *Dactylogyrus vastator* (Monogenea). Aquaculture 420–421, 302–307.
Zuskova, E., Piackova, V., Machova, J., Chupani, L., Steinbach, C., Stara, A., Velisek, J., 2018. Efficacy and toxicity of praziquantel in helminth-infected barbel (*Barbus barbus* L.). J. Fish. Dis. 41 (4), 643–649.