Universiti Malaysia Terengganu Journal of Undergraduate Research *eISSN: 2637-1138*
Volume 6 Number 2, April 2024: 62-75

HOST SPECIFICITY, INFECTION DYNAMICS, AND ALLERGENICITY IN *Anisakis* SPP. INFESTATION: A REVIEW

LAM RUO YI[1], SEE MING SHE[2], FAIZAH SHAROM-HARRISON[3], HAZLINA AHAMAD ZAKERI[1] AND NOR OMAIMA HARUN[1*]

[1]Faculty of Science and Marine Environment, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia.
[2]Faculty of Fisheries and Food Science, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia.
[3]BIOSES Research Interest Group, Faculty of Science and Marine Environment, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia.

**Corresponding author: omaima@umt.edu.my*
https://doi.org/10.46754/umtjur.v6i2.459
Submitted final draft: 7 April 2024 *Accepted: 7 April 2024* *Published:15 April 2024*

Abstract: Fish and seafood are important in providing protein to human diets. However, they are susceptible to contamination by various parasites, such as nematodes, cestodes, and trematodes. Among these, *Anisakis* spp. and other species of trematodes belonging to the Anisakidae family are commonly identified in fish and shellfish, posing a significant health risk. This contamination poses a substantial risk to public health, particularly with the increasing prevalence of these parasites in marine fish. The globalisation of cuisines, including sushi, is one of the factors causing this development. The risk of *Anisakis* contamination has increased due to the global popularity of sushi, a form of Japanese food that features raw or undercooked fish. Gastric anisakiasis is the primary infection in humans, caused by the penetration of L3 larvae into the gastric wall. However, the indefinite symptoms associated with anisakiasis make precise identification challenging, complicating efforts to effectively treat this health issue. This study reviewed the host specificity, risk factors, infection mechanisms, and infestation areas of *Anisakis* spp. Various reputable sources, including Google Scholar, PubMed Central, ScienceDirect, Springer Link, and the Wiley Online Library, were used to explore the diverse host preferences and the impact of environmental changes. The larvae of *Anisakis* spp. exhibit diverse host preferences and environmental changes like global warming make hosts more vulnerable. Inadvertent exposure to these parasites occurs when individuals consume raw or undercooked fish and seafood. An extremely serious threat is posed by allergic anisakiasis, characterised by severe symptoms such as respiratory arrest, shock, and collapse. Research focusing on bioactive substances capable of blocking or neutralising the excretions and secretions of *Anisakis* sp. should be encouraged. Metalloproteinases (MMPs) and serine proteases, in particular, show promise for minimising adverse effects and reducing dependency on medication in treating allergic anisakiasis. Further research and intervention techniques are essential if health issues associated with *Anisakis* exist.

Keywords: *Anisakis*, fish, allergen, infection dynamics, host specificity.

Introduction

The parasitic roundworm *Anisakis* spp. is commonly observed in marine fish (Nieuwenhuizen, 2016) and regularly parasitises adult marine mammals (Nieuwenhuizen & Lopata, 2013; Aibinu *et al.,* 2019), uses crustaceans, cephalopods, and fish as intermediate or paratenic hosts for its larvae. Three species, namely *Anisakis simplex* (sensu stricto), *Anisakis pegreffii*, and *Anisakis physeteris,* are reported to cause infections in humans from the genera of *Anisakis*, which also include Pseudoterranova, Contracaecum, and Hysterothylacium (Smith & Wootten, 1978; Aibinu *et al.,* 2019). However, humans can

become infected unintentionally while eating uncooked, improperly cooked, or otherwise contaminated fish or shellfish. As a result, dietary behaviours have been closely associated with the infection (Pampiglione *et al.,* 2002; Aibinu *et al.,* 2019). It is very likely that these parasites may infect their hosts and result in a variety of health issues.

The *Anisakis* spp. L3 larvae differ slightly in terms of morphology (Adroher-Auroux & Benitez-Rodriguez, 2020). A triangular mouth and triple lips surround the globular anterior part's boring teeth (Haryadi *et al.,* 2019; Sonko *et al.,* 2020; El Meghanawy *et al.,* 2021). Transverse cuticular striations are posterior to the lips and are surrounded by four pairs of labial papillae on the body (Sonko *et al.,* 2020; El Meghanawy *et al.,* 2021). According to observations of the ventriculus length and the presence of the mucron (Tunya *et al.,* 2020; Van Hien *et al.,* 2021), *Anisakis* spp. can be divided into Types I and II. Type I larvae have a longer ventriculus and a mucron, whereas Type II larvae have a shorter ventriculus and lack the mucron. Type I larvae are the ones that primarily infect humans (Cheypanya *et al.,* 2021). *Anisakis* spp. has a wide range of host specificities and complex life cycles, as illustrated in Figure 1 (Totoiu *et al.,* 2018).

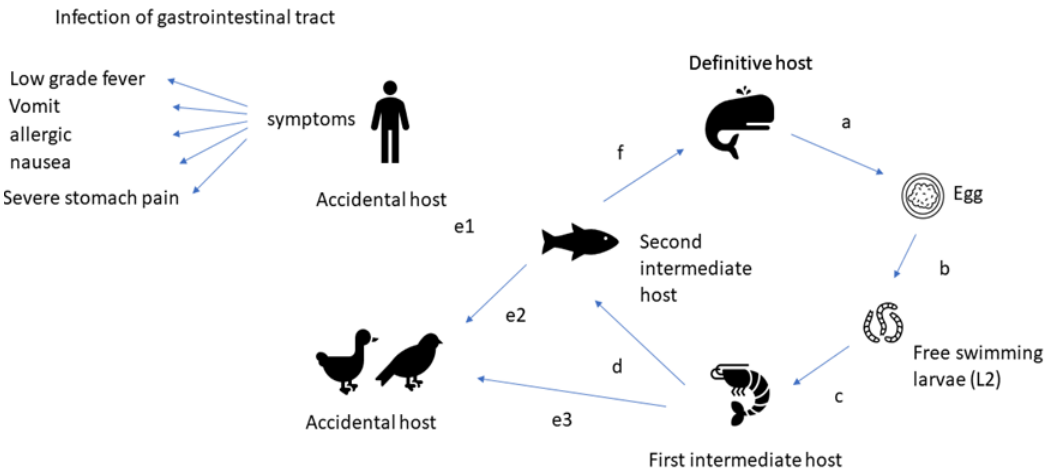

Figure 1: The *Anisakis* spp. life cycle. (a) Adults release eggs into the water along with the faeces of marine mammals; (b) The eggs hatch and release free-swimming L2; (c) The L2 is then ingested by first intermediate hosts and grows into L3; (d) e1, e2, and e3 infected intermediate and paratenic hosts are then ingested by accidental hosts; and (f) Infected second intermediate and paratenic hosts are then ingested by marine mammals (Totoiu *et al.,* 2018)

Numerous hosts are preferred by *Anisakis* spp. and undergo intricate life cycles (Totoiu *et al.,* 2018). Their eggs are released into the sea with the faeces of their hosts, primarily marine mammals, after they infest, mature, and breed (Caldeira *et al.,* 2021). These eggs develop into free-swimming L2 larvae, infecting intermediate hosts such as crustaceans (Baird *et al.,* 2014; Totoiu *et al.,* 2018). The L2 larvae eventually mature to L3 and are consumed by fish, squid, or cephalopods as paratenic hosts; humans and ducks that feed fish serve as accidental hosts (Aibinu *et al.,* 2019; Carvalho *et al.,* 2020; Fiorenza *et al.,* 2020). This parasitic infection is mainly brought on by eating raw or undercooked shellfish (Pampiglione *et al.,* 2002; Montalto *et al.,* 2005; Shamsi & Sheorey, 2018; Samanta & Choudhary, 2019).

When several larvae are ingested, they can migrate to various parts of the human body

(Mizumura *et al.,* 2018), leading to gastric anisakiasis in humans, where L3 larvae invade the stomach wall, potentially leading to death within 14 days if not treated (Shimamura *et al.,* 2016; Mizumura *et al.,* 2018). Intestinal anisakiasis results from larvae that are unable to penetrate the stomach wall and instead move to the intestines (Aibinu *et al.,* 2019). Through larval penetration, other organs like the spleen and throat may also become infected, causing ectopic or extra-gastrointestinal anisakiasis (Pampiglione *et al.,* 2002; Shamsi & Sheorey, 2018). Infections range from asymptomatic, where larvae remain in the gastrointestinal tract without harming the hosts (Cong & Elsheikha, 2021), to acute, characterised by severe stomach pain, nausea, vomiting, and low-grade fever (Montalto *et al.,* 2005), alongside possible allergic reactions (Aibinu *et al.,* 2019).

In summary, *Anisakis* spp. represent a significant health concern due to their complex life cycle involving various marine hosts and their capacity to cause anisakiasis in humans, primarily through consuming contaminated seafood. This review paper aims to elucidate the intricate life cycle of *Anisakis* spp., their morphological distinctions, particularly between Types I and II larvae, and the pathogenesis of anisakiasis in humans. Additionally, we will explore the epidemiological trends, diagnostic challenges, and current therapeutic strategies for managing anisakiasis. By providing a comprehensive overview of *Anisakis* spp. infections, including their transmission, clinical manifestations, and treatment approaches. This paper seeks to enhance our understanding of the risks posed by these parasites and inform public health strategies to mitigate their impact on human health.

Materials and Methods

Electronic databases, including Google Scholar, PubMed Central, ScienceDirect, Springer Link, and Wiley Online Library were used for this review. Only English-language pieces and full-version publications were considered. The magazine articles used ranged in date from 2004 to 2023. The key phrases were '*Anisakis'*, 'anisakiasis', 'fish', 'marine', and 'seafood', with an emphasis on 'The hosts of the *Anisakis* spp.', '*Anisakis* spp. infection in humans 'distribution of anisakiasis', and 'disease therapy'. Zotero was used as a data management tool to organise the vast amount of data that was gathered and utilised. The data were organised in accordance with the subtopics and keywords of this review study.

Results and Discussion

Host Specificity of Anisakis spp.

The host specificity of *Anisakis* spp. is extensive, and the degree of specificity can vary (Cheypanya *et al.,* 2021), correlated with how common their infection is. Due to their extensive host specificity, *Anisakis* spp. has the capacity to infect and infest a variety of marine species. Definitive hosts, intermediate hosts, paratenic hosts, and accidental hosts are four primary kinds of hosts that can be related. Whales, dolphins, seals, and sea lions are among the marine mammals that act as clear hosts (Totoiu *et al.,* 2018; Van Hien *et al.,* 2021). Infection with *Anisakis* spp. can affect a variety of fish species as intermediate and paratenic hosts, including cod, mackerel, salmon, saithe, redfish, blue whiting, pouting, anchovy, herring, and sardine (Adroher-Auroux & Benitez-Rodriguez, 2020). Furthermore, unintentional hosts like seabirds are susceptible to infection (Totoiu *et al.,* 2018).

Target Hosts

Anisakis like to infest terrestrial and marine creatures as their target hosts, and they often infest four different types of targeted hosts. Definitive hosts, intermediate hosts, paratenic hosts, and accidental hosts are the four categories into which the hosts can be divided (Figure 2). The majority of definitive hosts are marine mammals, which are crucial for developing and reproducing the *Anisakis* spp.

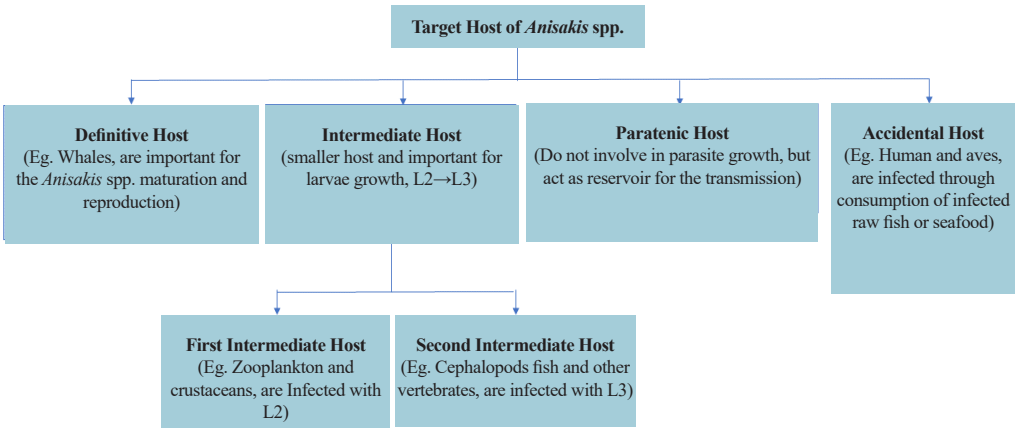

Figure 2: Summary of the target hosts of *Anisakis* spp., the definitive hosts which are important for *Anisakis* spp. life cycle is to be completed, intermediate host is for *Anisakis* spp. growth, the paratenic host, which does not involve *Anisakis* spp. growth, but act as a reservoir for the transmission and accidental hosts which are infected through the consumption of raw or und ercooked infected fish

Intermediate hosts are separated into first and second intermediate hosts and are important for *Anisakis* spp. larvae growth. First intermediate hosts are normally infected with stage-two larvae (L2), while second intermediate hosts are infected with stage-three larvae (L3) by ingesting infected first intermediate hosts (Shamsi, 2019). Paratenic hosts are not important for the *Anisakis* spp. life cycle, but are important for the transmission of the parasites by acting as a reservoir. This type of host can be from the second intermediate host when the larvae stay in their body longer before reaching the definitive host to complete the *Anisakis* spp. life cycle (Rolbiecki, 2002). Accidental hosts such as humans and Aves are usually infected with L3 by consuming raw or undercooked *Anisakis* spp. contaminated seafood (Adroher-Auroux & Benitez-Rodriguez, 2020).

Definitive Hosts

Definitive hosts, which are extensively widespread in colder and polar waters (Totoiu *et al.,* 2018), are often where the fourth-stage larvae (L4) and adult parasites are found. In order for parasites to feed, develop, and reproduce, they need definitive hosts. According to several studies (Table 1), most of these hosts are marine mammals, especially cetaceans (Quiazon *et al.,* 2013; Shamsi *et al.,* 2018; Shamsi *et al.,* 2019). *Anisakis* spp., L4 or adult stage, regularly congregate and embed themselves in the stomach mucosa and submucosa of cetaceans (Baptista-Fernandes *et al.,* 2017; Bao *et al*., 2019). Chai *et al*. (2005) stated that the population size of permanent hosts is a factor in determining the prevalence of *Anisakis* spp. in particular areas.

Table 1: Definitive hosts infected by *Anisakis* spp. at different body parts

Hosts	*Anisakis* spp.	Larvae Stage	Part of Infection	References
Definitive				
Dwarf sperm whale (*Kogia sima*)	*Anisakis brevispiculata, Anisakis typica,* two unknown *Anisakis* spp.	Pre-adult	Stomach	Quiazon *et al.,* 2013
Pygmy sperm whale (*Kogia breviceps*)	*Anisakis berlandi, Anisakis paggiae*	L4 / Adult	Stomach, intestine, oesophagus	Shamsi *et al.,* 2019
Whale (Species not stated)	*Anisakis paggiae*	Adult	Stomach, intestine, abdominal organs	Shamsi *et al.*, 2018

Intermediate Hosts

Since fish is usually edible, it can serve as both an intermediate host and a paratenic host simultaneously (Adroher-Auroux & Benitez-Rodriguez, 2020). As first intermediate hosts, larvae in the second stage can be found on crustaceans and zooplankton. The second intermediate hosts of the third-stage larvae are fish, other vertebrates, and cephalopods. Despite not being involved in forming *Anisakis* spp., paratenic hosts are crucial as reservoirs to increase the risk of infection (Rolbiecki, 2002).

Accidental Hosts

In contrast to other hosts, accidental hosts are typically the dead-end hosts for *Anisakis* spp., do not participate in the geographical movement of the parasites, and are crucial to the complex life cycle of *Anisakis* spp. These hosts get contaminated by unintentional intake of raw fish or seafood products (Nieuwenhuizen, 2016; Samanta & Choudhary, 2019; Sonko *et al*., 2020). Humans, occasionally Avians and reptiles, are the most frequent inadvertent hosts of *Anisakis* spp. (Pampiglione *et al.,* 2002; Santoro *et al.,* 2010; Carvalho *et al.,* 2020; Gentile e*t al.,* 2021) (Table 2). *Anisakis* spp. vulnerability was caused by the similarities in the gastrointestinal function between accidental hosts and marine mammals (Totoiu *et al.,* 2018).

Table 2: Accidental hosts infected by *Anisakis* spp. in various body sites

Hosts	*Anisakis* spp.	Larvae Stage	Part of Infection	References
Accidental				
Human	*Anisakis simplex*	L3	Ileum, mesentery, omentum, epiploic appendix, spleen	Pampiglione *et al.,* 2002
Loggerhead sea turtle (*Caretta caretta*)	*Anisakis pegreffii*	L3	Stomach, intestine, liver,	Santoro *et al.,* 2010
Muscovy duck (*Cairina moschata domestica*)	*Anisakis* spp.	L3	Oesophagus mucosa	Carvalho *et al.,* 2020

Detection Method for Anisakis spp. in Fish

Artificial digestion and the UV-press technique are used (Fioravanti *et al.*, 2021; Sánchez-Alonso *et al.*, 2021). The viscera, the abdominal cavity, and the fish fillet are visually inspected (Fioravanti *et al.,* 2021).

Hosts Factors of Anisakis spp. Infestation

The food web, immunity, and marine species are all impacted by global warming. Human health is impacted by improper food preparation and eating entire fish increases the danger since the intestines and viscera, typically infected with *Anisakis* spp., are not removed.

Anisakiasis: Infection of Anisakis spp.

One of the most dangerous fish-borne illnesses that affects people is anisakiasis (Shamsi, 2020). *Anisakis pegreffii* and *Anisakis simplex* (sensu stricto) are the two most prevalent species that infect humans (Adroher-Auroux & Benitez-Rodriguez, 2020; Sonko *et al.,* 2020; Cong & Elsheikha, 2021). Placing the larvae in the infected human body determines the type of anisakiasis, including allergic, ectopic, and gastrointestinal anisakiasis. Note that stomach pain, abdominal pain, vomiting, and bloody stools are typical symptoms of gastrointestinal anisakiasis caused by *Anisakis* larvae attaching to or entering the gastric or intestinal mucosa. Fever and sickness can happen occasionally. Ectopic anisakiasis is typically brought on by the invasion and migration of *Anisakis* larvae from the gastrointestinal system to other bodily parts, such as the spleen (Pampiglione *et al*., 2002; Shamsi & Sheorey, 2018), as the larvae are unable to be transferred.

Mechanisms and Sites of Infection

Mechanisms of Infection: Direct Tissue Damage

By releasing their proteolytic enzymes, *Anisakis* spp. directly destroy tissue, allowing it to pass through and infect the mucosa of the digestive tract (Łopieńska-Biernat *et al.,* 2020). The invasion of these parasites causes mechanical and biological harm to the affected person. The excretions or secretions of *Anisakis* species, including Metalloproteinases (MMPs) and serine proteases, are in charge of the breakdown of gastrointestinal extracellular matrix protein and fibrin created during penetration (Lee *et al.,* 2017; Cavallero *et al.,* 2022).

Subsequently, resulting in an invasive gastrointestinal anisakiasis (Baptista-Fernandes *et al.,* 2017) that indicates acute (abdominal pain, bloody diarrhoea, faintness, vomiting, and nausea) or chronic (abdominal peritonitis, urticaria, angioedema, anaphylaxis, and intestinal obstruction) symptoms (Aibinu *et al.,* 2019; Bao *et al.,* 2019; Amarnath *et al.,* 2021). Sometimes, invasive gastrointestinal anisakiasis may also lead to the formation of eosinophilic granuloma (Aibinu *et al.,* 2019), which leads to larvae death after a few weeks of infection (Baptista-Fernandes *et al.,* 2017). However, *Anisakis* spp. larvae may attach to multiple sites of the human digestive system simultaneously or in a metachronous manner (Mizumura *et al.,* 2018).

In addition, acute gastrointestinal anisakiasis is usually transient since it is found in the dying worm within a few weeks after ingesting infested fish (Marzano *et al.,* 2020). Acute gastric anisakiasis shows its symptoms shortly after consuming *Anisakis*-contaminated fish (Baptista-Fernandes *et al.,* 2017; Aibinu *et al.,* 2019). In contrast, an intestinal infection may take longer to show symptoms, normally within five days (Aibinu *et al.,* 2019). An intestinal infection usually happens when an individual is infected with multiple larvae, resulting in some larvae failing to attach to the stomach wall and being transported together with food to the intestine through peristalsis (Aibinu *et al.,* 2019).

Allergen Proteins Production

Excretory or secretory and somatic allergens are the two allergen proteins generated by live *Anisakis* spp. 90. Excretory or secretory allergens, such as Anis 1, Anis 4, Anis 5, Anis 6, Anis 7, Anis 8, Anis 9, and Anis 13, are more allergenic than somatic allergens, such as Anis

2 (paramyosin) and Anis 3 (tropomyosin), which have cross-reactivity with allergens from other invertebrates. Consequently, the somatic allergens are released after the *Anisakis* spp. larvae are killed by the formation of granuloma 91, but the secretory or excretory allergens are secreted by the living *Anisakis* spp. larvae at the afflicted portions 91. The allergen proteins of *Anisakis* spp., particularly Anis 4 (Aibinu *et al.,* 2019; Polimeno *et al.,* 2021), can occasionally trigger allergy reactions in consumers even after the parasite's larvae have been killed. This is because some allergen proteins are thermally and pepsin-resistant.

These allergens, released when the development of granulomas destroys larvae, react with those from dust mites and other invertebrates. This leads to misdiagnosis, most of the time, extreme thermal resistance, causing IgE and IgG to produce anaphylaxis, skin rash, and slight diarrhoea. According to Bao *et al.* (2019), airborne anisakiasis typically affects fishery and aquaculture workers and causes respiratory arrest, dermatitis, rhinoconjunctivitis, and asthma (Aibinu *et al.,* 2019; Bao *et al.,* 2019).

Asymptomatic Infection

Ingestion of *Anisakis* spp. larvae may result in asymptomatic infection, characterised by the absence of clinical symptoms due to larval infection without penetration of the gastrointestinal mucosa (Baptista-Fernandes *et al.,* 2017). However, larvae can induce sensitisation and increased IgE levels in affected individuals (Moneo *et al.,* 2017). Asymptomatic infection, particularly colonic anisakiasis (Zamora *et al*., 2021), is uncommon. Unfortunately, due to the lack of symptoms, misdiagnosis, and underdiagnosis, asymptomatic anisakiasis often goes untreated, increasing the risk of progression to chronic anisakiasis. This leads to abscess and granuloma formation (Zamora *et al.,* 2021).

Diagnosis of Anisakiasis

Early diagnosis of anisakiasis is crucial to prevent further migration and invasion of *Anisakis* larvae. For instance, misdiagnosis can lead to inappropriate treatment, risking patients with chronic infections such as the formation of granuloma (Mattiucci *et al.,* 2017; Polak *et al.,* 2020). Various tools can be used in anisakiasis diagnosis, including endoscopy, radiography, ultrasound, serum-specific anti-*Anisakis* IgE determination, and histological findings (Marzano *et al.,* 2020; Amarnath *et al.,* 2021). However, endoscopy, the most common method, is particularly effective for patients presenting with gastric pain or abdominal obstruction. This allows for direct detection and removal of larvae, providing individuals affected with a more accurate diagnosis and an appropriate course of treatment. It is important to consider the patient's eating habits and medical history in addition to the diagnostic approaches previously outlined (Marzano *et al.,* 2020; Amarnath *et al.,* 2021). Moreover, additional laboratory findings related to anisakiasis, such as leukocytosis and eosinophilia (Lee *et al.,* 2017) are also significant.

These comprehensive techniques give affected individuals a more accurate diagnosis and an appropriate course of treatment. In infected individuals, endoscopic examination may reveal superficial erosions and granulomas observed on the erythematous mucosa (Amarnath *et al.,* 2021). Other than that, ultrasound imaging may detect large ascites with elevated eosinophils in the ascitic fluid (Amarnath *et al.,* 2021) as well as small intestine dilation with localised oedema at small bowel folds (Amarnath *et al.,* 2021). Histological findings aid in diagnosis by observing larvae surrounded by eosinophils and histiocytes within the muscular layer of the ulcerated mucosa (Amarnath *et al.,* 2021). Confirmatory diagnosis can be achieved by detecting serum-specific IgE against *Anisakis* spp., indicating infection with a value up to 0.7 kU/L (Bao *et al.,* 2019).

The larval infection caused by *Anisakis* spp. is prone to misdiagnosis or underdiagnosis due to the absence of pathognomonic symptoms and inadequate diagnostic tools (Mattiucci *et al.,* 2017; Polak *et al.,* 2020). The non-specific

clinical characteristics of anisakiasis pose technical challenges, requiring highly skilled microscopists (Marzano *et al.,* 2020) for accurate diagnosis. Additionally, cross-reactivity between *Anisakis* allergen proteins and allergens from other nematodes or invertebrates can lead to a high number of false-positive results in specific immunoglobulin tests (Aibinu *et al.,* 2019; Marzano *et al.,* 2020). The common symptoms of anisakiasis, such as severe gastrointestinal disturbance, which is non-specific, result in misdiagnosis as appendicitis, gastric ulcers and tumours (Audicana *et al.,* 2017; Marzano *et al.,* 2020), inflammatory bowel diseases, ileitis, and diverticulitis (Aibinu *et al.,* 2019). Besides, the allergic reactions caused by the consumption of *Anisakis*-contaminated fish are also often misdiagnosed as food and drug allergies (Audicana *et al.,* 2017).

Human Immune Responses against Anisakis spp. Infection

The innate immunity of an infected patient is triggered by the presence of *Anisakis* spp. However, due to the parasites' greater size, phagocytic cells are unable to directly swallow the parasites (Motran *et al*., 2018). Thus, Antibody-dependent Cellular Cytotoxicity (ADCC), a mechanism of human immunity, is crucial to the parasites' deaths. As a result of *Anisakis* spp. penetration, tissues damaged by chronic anisakiasis release a variety of immune cells, including basophils, eosinophils, macrophages, mast cells, and Dendritic Cells (DCs) (Motran *et al.,* 2018; Napoletano *et al.,* 2018).

The DCs are essential in the immune responses against anisakiasis because they identify and carry allergen proteins or parasite antigens to T cells to trigger Type II helper T cells (Th2) responses, phagocytosis, inflammation, and cytokine modulation (Motran *et al.,* 2018). (Napoletano *et al.,* 2018). Note that eosinophilic granuloma forms at the larval attachment sites, killing the larvae (Adroher-Auroux & Benitez-Rodriguez, 2020). To overcome the host immunity, the live larvae must cause the DCs to undergo apoptosis (Napoletano *et al.,* 2018). The position of McSorley and Maizels (2012), who suggested that the degree of disease in an infected patient may be connected to the parasite burden, has been supported by this finding. The immune escape strategy used by parasites may cause a low pathology level.

Treatment of Anisakiasis

There are three types of treatment for anisakiasis: Physical removal, anthelmintic treatment, and surgery (Figure 3). The choice of treatment depends on various factors, including the location and severity of the infection. The most common approach for treating stomach anisakiasis involves physically removing larvae using endoscopic techniques such as gastroscopy for gastric infection or colonoscopy for intestinal infection. This method allows for direct visualisation and removal of larvae using forceps or Roth nets (Cong & Elsheikha, 2021). Pharmacological therapy is not required if an infected person recovers after removing the larvae within a few hours (Adroher-Auroux & Benitez-Rodriguez, 2020). Early diagnosis and prompt removal of *Anisakis* spp. larvae are crucial to preventing the progression of the infection to a chronic form (Mattiucci *et al.,* 2017). Apart from removal, identification and addressing eosinophilic granuloma formation resulting from allergic reactions is essential in preventing chronic anisakiasis (Mattiucci *et al.,* 2017).

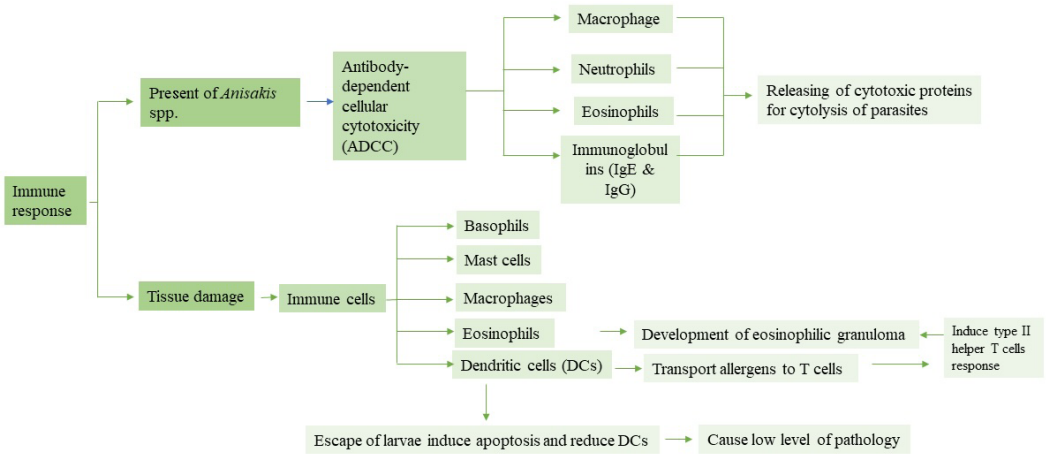

Figure 3: Summary of treatment of human anisakiasis. Direct larvae removal is the most common treatment, which requires endoscopy and forceps for removal and is usually applied to the gastrointestinal infection. Anthelmintic treatment may not be required if the condition of the patient becomes better

Pharmaceutical treatment of anisakiasis may not be necessary if the patient's condition improves following larval removal within a few hours (Adroher-Auroux & Benitez-Rodriguez, 2020). However, anthelmintic drugs are commonly prescribed to enhance treatment efficacy (Mangmee *et al.,* 2020), often in combination, such as albendazole with thiabendazole or flubendazole (Shimamura *et al.,* 2016). Despite their use in eliminating parasitic larvae, anthelmintics may not be fully effective, and their mechanisms of action on *Anisakis* spp. larvae remain unclear. Additionally, some patients may experience side effects from anthelmintic drugs, underscoring the need for alternative treatment options with fewer adverse effects. Notably, a study presented that thiabendazole is more effective against parasitic larvae compared to flubendazole (Mangmee *et al.*, 2020).

However, these drugs are not fully effective against the infection (Adroher-Auroux & Benitez-Rodriguez, 2020), and their mechanisms of action of the drugs on *Anisakis* spp. larvae remain unclear (Polak *et al.,* 2020). In addition, some patients who apply thiabendazole are affected by its side effects (Mangmee *et al.*, 2020), including dizziness, numbness, fever, ringing ears, and unusual urine odour (Cunha, 2021). As a result, current studies are focusing on essential oils derived from plants and their components as potential alternatives to replace anthelmintic drugs (Adroher-Auroux & Benitez-Rodriguez, 2020). These bioactive compounds are being investigated for their efficacy and potential to minimise side effects in anisakiasis treatment.

The severe cases of anisakiasis can are characterised by the presence of larvae that are deeply embedded in the mucosa (Choi *et al.,* 2017) or at the ectopic sites (Hochberg & Hamer, 2010; Nieuwenhuizen, 2016). This situation may require surgical intervention (Nieuwenhuizen, 2016). Surgical removal becomes essential when physical extraction via endoscopy is not feasible. However, it is important to note that severe cases of anisakiasis may sometimes be misdiagnosed as intestinal obstructions. Therefore, diagnostic imaging is vital in accurately diagnosing and managing intestinal anisakiasis to avoid unnecessary surgeries (Joo *et al.,* 2019).

The management of anisakiasis benefits from a multidisciplinary approach

involving gastroenterologists, infectious disease specialists, surgeons, and other healthcare professionals. Hence, collaborative efforts facilitate comprehensive evaluation, individualised treatment plans, and ongoing research into emerging treatment modalities. Future directions in managing anisakiasis include refining diagnostic techniques, optimising treatment strategies, and exploring innovative therapeutic approaches. By advancing our understanding of this parasitic infection and implementing multidisciplinary care, clinicians and researchers can improve patient outcomes and reduce the global burden of anisakiasis.

Conclusions

In conclusion, *Anisakis* spp. larvae have broad host specificity and are susceptible to humans. In marine animals, the prevalence of *Anisakis* spp. infestation can be affected by environmental changes, such as global warming. Meanwhile, the human risk factor for infection is normally the consumption of undercooked or raw fish or seafood. There are two types of allergen proteins: (a) Excretory or secretory allergens and (b) Somatic allergens. Excretory or secretory allergens are more allergenic compared to somatic allergens and are thermal and pepsin-resistant, especially Anis 4, which cannot be destroyed even though fish is completely cooked. Meanwhile, somatic allergens are normally found to be cross-reactive with allergens produced by other vertebrates, which usually causes misdiagnosis. Parasite detection methods are usually ignored by the fishery industry and the public due to high operating costs. Moreover, human anisakiasis is distributed worldwide due to the internationalisation of cuisines from different countries. Allergic anisakiasis is considered dangerous as it will lead to respiratory arrest, shock, and collapse.

Despite the significant health risks associated with *Anisakis* spp. infestation, parasite detection methods are often overlooked due to high costs and technical challenges. This oversight contributes to the global distribution of human anisakiasis, facilitated by the internationalisation of cuisines. Therefore, addressing the challenges associated with parasite detection methods is essential for effectively preventing and controlling anisakiasis.

In order to promptly intervene and prevent human infection, it is necessary to develop more precise detection methods for *Anisakis* spp. larvae observed in fish and seafood items. Other diagnostic modalities that are affordable and available to the public, as well as the fishing industry, should also be investigated further. In addition, studies on bioactive substances such as serine proteases and MMPs that can inhibit or inactivate the excretions or secretions of *Anisakis* spp. show promise for lessening the negative effects of medication and curing allergic anisakiasis by itself. We can better safeguard public health and lessen the worldwide burden of anisakiasis by improving our capacity to identify and control *Anisakis* spp. infestations.

Data management: Zotero, data is organised according to the subtopics and keywords of this review paper.

Acknowledgement

We thank Universiti Malaysia Terengganu for providing funding support for this project (UMT/RIG/2019/55192/4).

References

Adroher-Auroux., F. J., & Benitez-Rodriguez. (2020). Anisakiasis and *Anisakis*: An underdiagnosed emerging disease and its main etiological agents. *Research in Veterinary Science*, *132*, 535-545. https://doi.org/10.1016/j.rvsc.2020.08.003

Aibinu, I. E., Smooker, P. M., & Lopata, A. L. (2019). *Anisakis* Nematodes in fish and shellfish- from infection to allergies. *International Journal for Parasitology: Parasites and Wildlife (IJP-PAW)*, *9*, 384-393. https://doi.org/10.1016/j.ijppaw.2019.04.007

Amarnath, S., Deeb, L., Philipose, J., Zheng, X., & Gumaste, V. A. (2021). A comprehensive review of infectious granulomatous diseases of the gastrointestinal tract. *Gastroenterology Research and Practice, 2021,* 1-20. https://doi.org/10.1155/2021/8167149

Audicana, T., Italo, G., & Areso, N. (2017). *Anisakis simplex*, a new hero in the Anaphylaxis Scene. *SM Emergency Medicine and Critical Care Journal*, *1*, 1-6. https://doi.org/10.36876/smem.1008

Baird, F. J., Gasser, R. B., Jabbar, A., & Lopata, A. L. (2014). Foodborne anisakiasis and allergy. *Molecular and Cellular Probes*, *28*, 167-174. https://doi.org/10.1016/j.mcp.2014.02.003

Bao, M., Pierce, G. J., Strachan, N. J. C., Pascual, S., González-Muñoz, M., & Levsen, A. (2019). Human health, legislative and socioeconomic issues caused by the fish-borne zoonotic parasite *Anisakis*: Challenges in risk assessment. *Trends in Food Science and Technology*, *86*, 298-310. https://doi.org/10.1016/j.tifs.2019.02.013

Baptista-Fernandes, T., Rodrigues, M., Castro, I., Paixão, P., Pinto-Marques, P., Roque, L., Belo, S., Ferreira, P. M., Mansinho, K., & Toscano, C. (2017). Human gastric hyperinfection by *Anisakis simplex*: A severe and unusual presentation and a brief review. *International Journal of Infectious Diseases*, *64*, 38-41.

Caldeira, A. J. R., Pereira, A. C. P., & Santos, M. J. (2021). *Anisakis* notification in fish: An assessment of the cases reported in the European Union Rapid Alert System for Food and Feed (RASFF) database. *Food Control*, *124*, 107913. https://doi.org/10.1016/j.foodcont.2021.107913

Carvalho, E. L., de, Santana, R. L. S., Gonçalves, E. C., Pinheiro, R. H. da S., & Giese, E. G. (2020). First report of Anisakis sp. (Nematoda: Anisakidae) parasitizing Muscovy duck in Marajó Island, State of Pará, Brazil. Revista Brasileira de Parasitologia Veterinaria, 29, e020319. https://doi.org/10.1590/s1984-29612020015

Cavallero, S., Bellini, I., Pizzarelli, A., & D'Amelio, S. (2022). What do *In Vitro* and *In Vivo* Models tell us about Anisakiasis? New tools still to be explored. *Pathogens, 11*(3), 285. https://doi.org/10.3390/pathogens11030285

Cheypanya, V., Wongsawad, P., Wongsawad, C., & Nantarat, N. (2021). Morphological study and molecular epidemiology of *Anisakis* larvae in mackerel fish. *Asian Pacific Journal of Tropical Medicine*, *14*, 214. https://doi.org/10.4103/1995-7645.315900

Choi, S. K., Kim, C. K., Kim, S. H., & Jo, D. I. (2017). Anisakiasis involving the oral mucosa. *Archives of Craniofacial Surgery, 18*, 261-263. https://doi.org/10.7181/acfs.2017.18.4.261

Cong, W., & Elsheikha, H. M. (2021). Biology, epidemiology, clinical features, diagnosis, and treatment of selected fish-borne parasitic zoonoses. *Yale Journal of Biology and Medicine*, *94*, 297-309.

Cunha, J. P. (2021). *Mintezol (Thiabendazole) side effects drug centre.* RxList. URL Accessed December 20, from https://www.rxlist.com/mintezol-side-effects-drug-center.htm#overview

El Meghanawy, R. A., E. I., E. T., Salim Dalia, A., & Abdel Aziz, A. R. (2021). Epidemiological, morphological, and molecular characterization of *Anisakis simplex* (sensu stricto) in *Clupea harengus* from Egypt. *Veterinary Parasitology: Regional Studies and Reports*, *24*, 100574. https://doi.org/10.1016/j.vprsr.2021.100574

Fioravanti, M. L., Gustinelli, A., Rigos, G., Buchmann, K., Caffara, M., Pascual, S., & Pardo, M. Á. (2021). Negligible risk of zoonotic anisakid nematodes in farmed fish from European mariculture, 2016 to 2018. *Eurosurveillance*, *26*, 1900717. https://doi.org/10.2807/1560-7917.ES.2021.26.2.1900717

Fiorenza, E. A., Wendt, C. A., Dobkowski, K. A., King, T., Pappaionou, M., Rabinowitz, P., Samhouri, J. F., & Wood, C. L. (2020). It's a wormy world: Meta-analysis reveals several decades of change in the global abundance of the parasitic nematodes *Anisakis* spp. and *Pseudoterranova* spp. in marine fishes and invertebrates. *Global Change Biology*, *26*, 2854-2866. https://doi.org/10.1111/gcb.15048

Gentile, A., Amato, T., Gustinelli, A., Fioravanti, M. L., Gambino, D., Randazzo, V., Caracappa, G., Vicari, D., & Arculeo, M. (2021). Helminth infection of the Loggerhead Sea Turtle Caretta caretta along the Coasts of Sicily and the North West Adriatic Sea. *Animal* (Basel), *11*(5), 1408. https://doi.org/10.3390/ani11051408

Haryadi, L., Suprayitno, E., Aulani, A., Amin, M., & Hariati, A. (2019). Identification of Anisakid nematode L3 larvae infection on Skipjack Tuna (*Katsuwonus pelamis L.* from Kupang waters, East Nusa Tenggara of Indonesia. *Russian Journal of Agricultural and Socio-Economic Sciences (RJOAS)*, *92*, 305-312. https://doi.org/10.18551/rjoas.2019-08.35

Hochberg, N. S., & Hamer, D. H. (2010) Anisakidosis: Perils of the deep. *Clinical Infectious Diseases*, *51*, 806-812. https://doi.org/10.1086/656238

Joo, S. K., Kim, J. W., Kim, B. G., Kim, W., Lee, J. K., & Lee, K. L. (2019). Clinical and endoscopic features of Colonic Anisakiasis in Korea. *Korean Journal of Parasitology*, *57*, 411-416. https://doi.org/10.3347/kjp.2019.57.4.411

Lee, J. D., Chung, L. Y., Lin, R. J., Wang, J. J., Tu, H. P., & Yen, C. M. (2017). Excretory/secretory proteases and mechanical movement of *Anisakis pegreffii* infective larvae in the penetration of BALB/c mice gastrointestine. *The Kaohsiung Journal of Medical Sciences*, *33*, 594-601.

Łopieńska-Biernat, E., Stryiński, R., Polak, I., Pawlikowski, B., Pawlak, J., & Podolska, M. (2020). Effect of freezing on the metabolic status of L3 larvae of *Anisakis simplex* s. s. *Infect. Genetics Selection Evolution*, *82*, 104312. https://doi.org/10.1016/j.meegid.2020.104312

Mangmee, S., Adisakwattana, P., Tipthara, P., Simanon, N., Sonthayanon, P., & Reamtong, O. (2020). Lipid profile of *Trichinella papuae* muscle-stage larvae. *Scientific Reports*, *10*, 10125. https://doi.org/10.1038/s41598-020-67297-8

Marzano, V., Pane, S., Foglietta, G., Mortera, S. L., Vernocchi, P., Muda, A. O., & Putignani, L. (2020). Mass Spectrometry Based-Proteomic Analysis of *Anisakis* spp.: A preliminary study towards a new diagnostic tool. *Genes (Basel)*, *11*(6), 693. https://doi.org/10.3390/genes11060693

Mattiucci, S., Paoletti, M., Colantoni, A., Carbone, A., Gaeta, R., Proietti, A., Frattaroli, S., Fazii, P., Bruschi, F., & Nascetti, G. (2017). Invasive anisakiasis by the parasite *Anisakis pegreffii* (Nematoda: Anisakidae): Diagnosis by real-time PCR hydrolysis probe system and immunoblotting assay. *BMC Infectious Diseases*, *17*, 1-9. https://doi.org/10.1186/s12879-017-2633-0

McSorley, H. J., & Maizels, R. M. (2012). Helminth infections and host immune. *Regulation Clinical Microbiology Reviews*, *25*(4), 585-608. https://doi:10.1128/CMR.05040-11

Mizumura, N., Okumura, S., Tsuchihashi, H., Ogawa, M., & Kawasaki, M. (2018). A second attack of *Anisakis*: Intestinal Anisakiasis following Gastric Anisakiasis *ACG Case Reports Journal*, *5*, e65. https://doi.org/10.14309/crj.2018.65

Moneo, I., Carballeda-Sangiao, N., & González-Muñoz, M. (2017). New perspectives on the diagnosis of allergy to *Anisakis* spp. *Current Allergy and Asthma Reports*, *17*, 27. https://doi.org/10.1007/s11882-017-0698-x

Montalto, M., Miele, L., Marcheggiano, A., Santoro, L., Curigliano, V., Vastola, M., & Gasbarrini, G. (2005). *Anisakis* infestation: A case of acute abdomen mimicking Crohn's disease and eosinophilic gastroenteritis. *Digestive and Liver Disease*, *37*, 62-64. https://doi.org/10.1016/j.dld.2004.05.014

Motran, C. C., Silvane, L., Chiapello, L. S., Theumer, M. G., Ambrosio, L. F., Volpini, X., Celias, D. P., & Cervi, L. (2018). Helminth infections: Recognition and modulation of the immune response by innate immune cells. *Frontiers in Immunology*, *9*, 664. https://doi.org/10.3389/fimmu.2018.00664

Napoletano, C., Mattiucci, S., Colantoni, A., Battisti, F., Zizzari, I. G., Rahimi, H., Nuti, M., & Rughetti, A. (2018). *Anisakis pegreffii* impacts differentiation and function of human dendritic cells. *Parasite Immunology*, *40*, e12527. https://doi.org/10.1111/pim.12527

Nieuwenhuizen, N. E. (2016). *Anisakis*-Immunology of a foodborne parasitosis. *Parasite Immunology*, *38*, 548-557. https://doi.org/10.1111/pim.12349

Pampiglione, S., Rivasi, F., Criscuolo, M., De Benedittis, A., Gentile, A., Russo, S., Testini, M., & Villani, M. (2002). Human Anisakiasis in Italy: A report of eleven new cases. *Pathology – Journal Research and Practice*, *198*, 429-434. https://doi.org/10.1078/0344 -0338-00277

Polak, I., Łopieńska-Biernat, E., Stryiński, R., Mateos, J., & Carrera, M. (2020). Comparative Proteomics Analysis of *Anisakis simplex* s.s. - Evaluation of the response of invasive larvae to ivermectin. *Genes*, *11*, 710. https://doi.org/10.3390/genes11 060710

Polimeno, L., Lisanti, M. T., Rossini, M., Giacovazzo, E., Polimeno Lucrezia Debellis, L., Ballini., A. Topi, S., & Santacroce, L. (2021). *Anisakis* allergy: Is aquacultured fish a safe and alternative food to wild-capture fisheries for *Anisakis simplex* - Sensitized patients? *Journal of Biology*, *10*, 106. https://doi.org/10.3390/biology 10020106

Rolbiecki, L. (2002). On the role of paratenic hosts in the life cycle of the nematode *Anguillicola crassus* in the Vistula Lagoon, Poland. *Acta Ichthyologica Et Piscatoria*, *32*, 109-116. https://doi.org/10.3750/AIP 2002.32.2.01

Samanta, M., & Choudhary, P. (2019). Chapter 7 - Safety of fish and seafood. In Singh, R. L., Mondal, S. (Eds.), *Food safety and human health* (pp. 169-187). Academic Press. https://doi.org/10.1016/B978-0-12-816333-7.00007-2

Sánchez-Alonso, I., Carballeda-Sangiao, N., Rodríguez, S., Tejada, M., Navas, A., Arcos, S. C., González-Muñoz, M., & Careche, M. (2021). *Anisakis simplex* (s.l.) resistance to the action of gastric enzymes depends upon previous treatments applied to infected fish mince and affects antigen release. *Journal of the Science of Food and Agriculture*, *101*, 3908-3916. https://doi.org/10.1002/jsfa.11031

Santoro, M., Badillo, F. J., Mattiucci, S., Nascetti, G., Bentivegna, F., Insacco, G., Travaglini, A., Paoletti, M., Kinsella, J. M., Tomás, J., *et al*. (2010). Helminth communities of Loggerhead Turtles (*Caretta Caretta*) from Central and Western Mediterranean Sea: The importance of host's ontogeny. *Parasitology International Journal*, *59*, 367-375. https://doi.org/10.1016/j.parint.2010.04.009

Santoro, M., Di Nocera, F., Iaccarino, D., Cipriani, P., Guadano Procesi, I., Maffucci, F., Hochscheid, S., Blanco, C., Cerrone, A., Galiero, G., Nascetti, G., & Mattiucci, S. (2018). Helminth parasites of the dwarf sperm whale Kogia sima. *Diseases of Aquatic Organisms*, *129*(3), 175-182. https://doi.org/10.3354/dao03251

Shamsi, S. (2019). Parasite loss or parasite gain? Story of Contracaecum nematodes in

antipodean waters. *Parasite Epidemiology Control, 4,* e00087. https://doi.org/10.1016/j.parepi. 2019.e00087

Shamsi, S. (2020). Seafood-borne parasites in Australia: Human health risks, fact or fiction? *Microbiology Australia, 41*(1), 33-37.

Shamsi, S., & Sheorey, H. (2018). Seafood-borne parasitic diseases in Australia: Are they rare or underdiagnosed? *Internal Medicine Journal*, *48*, 591-596. https://doi.org/10.1111/imj.13786

Shimamura, Y., Muwanwella, N., Chandran, S., Kandel, G., & Marcon, N. (2016). Common symptoms from an uncommon infection: Gastrointestinal Anisakiasis. *Canadian Journal of Gastroenterology and Hepatology*, e5176502. https://doi.org/10.1155/ 2016/5176502

Sonko, P., Chih-Cheng Chen, S., Chou, C. M., Huang, Y. C., Hsu, S. L., Barčák, D., Oros, M., & Fan, C.-K. (2020). Multidisciplinary approach in study of the zoonotic *Anisakis* larval infection in the blue mackerel (*Scomber australasicus*) and the largehead hairtail (*Trichiurus lepturus*) in Northern Taiwan. *Journal of Microbiology, Immunology and Infection, 53*(6), 1021-1029. https://doi.org/10.1016/j.jmii.2019.04.012

Totoiu, A., Nenciu, M.-I., & Nicolae, C. G. (2018). Assessing the inter-relations between fish health and stock status on human health and consumer perception. *Scientific Papers, Series D. Animal Science*, *61*(2), 268-73. https://doi.org/10.1016/j fishres.2017.06.018

Tunya, R., Wongsawad, C., Wongsawad, P., & Chai, J.-Y. (2020). Morphological and molecular characteristics of Anisakis typica larvae in two species of Threadfin Bream, Nemipterus hexodon and Nemipterus japonicus, from the Gulf of Thailand. *Korean Journal of Parasitology, 58,* 15-25. https://doi.org/10.3347/kjp.2020.58.1.15

Van Hien, H., Thi Dung, B., Ngo, H. D., & Doanh, P. N. (2021). First morphological and molecular identification of third-stage larvae of *Anisakis typica* (Nematoda: Anisakidae) from marine fishes in Vietnamese water. *Journal of Nematology*, *53*, e2021-10. https://doi.org/10.21307/jofnem-2021-01

Zamora, V., Carlos, Andreu-Ballester, J., Rodero, M., & Cuéllar, C. (2021). *Anisakis simplex*: Immunomodulatory effects of larval antigens on the activation of toll like receptors. *Journal of International Immunopharmacology*, *100*, 108120. https://doi.org/10.1016/j.intimp.2021.108120