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Review article

Concentration ciguatoxins in fillet of fish: A global systematic review and meta-analysis

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A R T I C L E I N F O

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A B S T R A C T

In the current study, an attempt was made to meta-analyze and discuss the concentration of ciguatoxins (CTXs) in fillets of fish based on country and water resources subgroups. The search was conducted in Scopus and PubMed, Embase and Web of Science to retrieve papers about the concentration of CTXs in fillet fish until July 2022. Meta-analysis concentration of CTXs was conducted based on countries and water resources subgroups in the random effects model (REM). The sort of countries based on the pooled concentration of CTXs was Kiribati (3.904 μg/kg) > Vietnam (1.880 μg/kg) > Macaronesia (1.400 μg/kg) > French (1.261 μg/kg) > China (0.674 μg/kg) > Japan (0.572 μg/kg) > USA (0.463 μg/kg) > Spain (0.224 μg/kg) > UK (0.170 μg/kg) > Fiji (0.162 μg/kg) > Mexico (0.150 μg/kg) > Australia (0.138 μg/kg) > Portugal (0.011 μg/kg). CTXs concentrations in all countries are higher than the safe limits of CTX1C (0.1 μg/kg). However, based on the safe limits of CTX1P, the concentrations of CTXs in just Portugal meet the regulation level (0.01 μg/kg). The minimum and maximum concentrations of CTXs were as observed in Selvagens Islands (0.011 μg/kg) and St Barthelemy (7.875 μg/kg) respectively. CTXs concentrations in all water resources are higher than safe limits of CTX1C (0.1 μg/kg) and CTX1B (0.01 μg/kg). Therefore, it is recommended to carry out continuous control pans of CTXs concentration in fish in different countries and water sources.

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1. Introduction

Fish of good quality is among the healthiest foods on the planet with high nutritional value[1–3]. Fish is a source of protein and several vital nutrients of public health importance consisting of vitamins (nicotinamide (B3), pyridoxine (B6) and cobalamin (B12), minerals (calcium, iron, selenium, zinc, etc.), and essential omega-3 polyunsaturated fatty acids (PUFAs) [4]. Findings from cohort studies suggest that each of these can improve physical and mental health, and cognitive development, improve maternal and child health outcomes, strengthen the immune system, and even can reduce the risk of diseases such as heart disease, cancer, diabetes, dementia, osteoporosis, psoriasis, lupus, arthritis, retinopathy, and other chronic and inflammatory diseases [5,6].

Global fish consumption has increased 3.1% average annual rate [7]. Globally, fish provided more than 3.3 billion people with 20% of their average per capita intake of animal proteins [8], reaching 50% or more in countries such as Sri Lanka, Bangladesh, the Gambia, Cambodia, Ghana, Indonesia, and Sierra Leone [5].

Increasing microbail and chemical pollution has become a global concern [9–13]. Exposure to microbial and chemical pollution in the environment can have advearse health effects [14–18]. Discharge of urban and industrial wastewater content of heavy metals, increased use of pesticides in agriculture, etc. have increased health risks [19–23].

With increasing population and decreasing food resources and also the industrialization of countries [24], concern on entry of contaminats such as oxic polycyclic polyethers [25], metconazole [26], heavy metal [27–31], mycotoxins [32–38] into the food chain and endangering food safety and security has increased [24,39].

Various contaminants or toxins can be presented in the environment [40–44], one of which is ciguatoxins (CTXs). CTXs enter the marine food web through herbivorous fish or benthic invertebrates that consume macroalgae content of dinoflagellate microorganism. The majority of these creatures are crucial food items for carnivorous species, and top fish predators bioaccumulate poisons, ultimately reaching humans when these toxins containing animals are consumed [25]. These toxins bind to voltage-gated sodium and potassium channels in a competitive manner with varying potencies [45]. They are extremely lipophilic, heat-stable polycyclic ether compounds with molecular weights of ~1000–1150 Da [46]. Since CTXs have no taste, color, or smell, it is still very challenging to distinguish ciguatoxic fish [47]. The structure of CTXs varies depending on where they are found geographically, so they are divided into three categories: ciguatoxins from the Pacific Ocean (*P*-CTX), Caribbean Sea (*C*-CTX), and Indian Ocean (I-CTX) [45]. Additionally, fish metabolically alter dinoflagellate toxins, which results in the production of a large number of structurally related CTX congeners [48]. The European Food Safety Authority (EFSA) and the United States Food and Drug Administration (US FDA) both consider CTX1B to be the most potent toxin, and they have set the recommended safety limit for CTXs in fish for human consumption at 0.01 ng CTX1B toxin equivalent/g fish tissue (0.01 ppb CTX1B equivalent) (US FDA) [49]. Ciguatera, a serious health danger that has led to significant harvest limits to avoid goods with primary health risks, is a big barrier to achieving this goal [49,50]. One of the most common marine poisoning related to fish consumption is Ciguatera poisoning (CP), which is caused by consuming fish contaminated with neurotoxins such as CTXs [51]. The prevalence of CP has increased significantly in recent years, the study of Skinner et al. showed that the incidence of CP increased by 60% from 1998 to 2008 compared to 1973–1983 [52].

Despite the variety of symptoms, the inversion of heat perception (also known as allodynia), together with paresthesia, exhaustion, articular and muscle pain, vomit, and diarrhea, is the most distinctive hallmark of ciguatera fish poisoning (CFP) [53]. Additionally, regional variations have been noted, with neurological symptoms typically outweighing stomach disturbances and persisting in the Pacific, while gastric symptoms are more common in the Atlantic endemic regions [54,55]. Indian CFP results in normal CFP

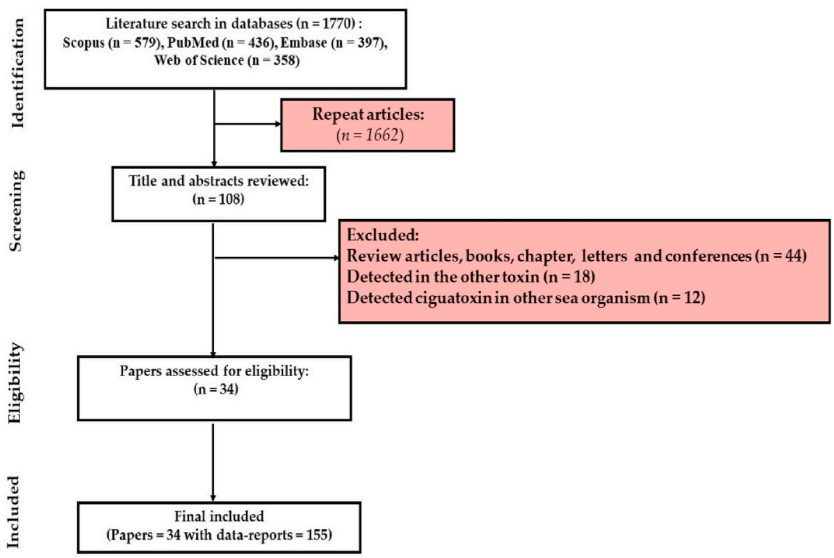

Fig. 1. Selection process of papers based on PRISMA.

symptoms, including hallucinations, sadness, and nightmares [48]. Numerous fish species, particularly in tropical and subtropical regions, have been linked to CFP, each having distinct eating habits, size, and life spans [56]. Fortunately, this illness, which is marked by digestive, neurological, and circulatory issues, seldom results in death [57]. The ailment affects between 10,000 and 50,000 persons yearly. However, this number is likely significantly understated given the prevalence of unreported cases from distant locations and misdiagnosis [58].

Although many studies have been conducted about the concentration of CTXs in fish in the world [59–65], no systematic review and meta-analysis were found. On the other hand, meta-analysis of concentration can provide more accurate and reliable results of CTXs in fish in different places of the world. Also, meta-analysis of concentration CTXs in fish can help researchers in the interpretation of mortality or disability rates related to the ingestion of the CTXs. Main aim of current study was metanalysis concentration of CTXs in fillets of fish based on countries and water resources subgroups.

2. Material and method

2.1. Search strategy

The process selection of papers was performed based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Fig. 1) [66,67]. International databases including Scopus and PubMed, Embase, and Web of Science are used to search in order to retrieve papers on the concentration ciguatoxins in fish until July 2022. Keywords were consist of " ciguatoxins " OR “toxic polycyclic polyethers” OR ″ CTXs " AND “marine foods” OR “fish” OR ″ Carp fish” OR “seafood”. The reference list of retrieved papers was screened to find missed papers. Disagreement between authors in selecting or rejecting a paper was resolved by the final comment of the corresponding author.

2.2. Inclusion of criteria and data extraction

Inclusion criteria were 1) present mean or range concentration of CTXs, 2) descriptive study and 3) detection of CTXs in the fillets of fish. Books, Book chapters, Letters to the editor, Review papers, Conferences, and investigations that detected CTXs in the other parts of fish were excluded. Type of fish, Family, Source, County, Sample size, Mean and standard deviation concentration CTXs, Method of detection and limit of detection (LOD) were extracted from retrieved papers (Appendix 1).

2.3. Meta-analysis concentration of CTXs

The meta-analyzed concentration of CTXs in fillet fish was performed using average and standard error [68]. The I^2 statistic was applied to determine the heterogeneity of data. In our study, the I^2 index was higher than 50% [69–71]; hence, the random effects model (REM) was used for meta-analysis of CTXs based on countries and source subgroups. Meta-analysis of data were performed using stata14.0 (Stata, College Station, TX, USA).

3. Results and discussion

A search was conducted in international databases and 1770 papers were obtained after removing repeated papers and screening based on the title and abstract and full text of the manuscript, 34 papers with 155 data reports (sample size: 2869) were included in the meta-analysis (Fig. 1 and Table 1S). The sort of countries based on the pooled concentration of CTXs was Kiribati (3.904 μg/kg) >

Table 1
Meta-analysis concentration of ciguatoxin in fish based on countries (μg/kg).

Country	Number of studies	ES	Lower	Upper	Weight (%)	Country	Heterogeneity statistic	Degrees of freedom	p value	I^2
Australia	2	0.138	0.122	0.153	2.43	Australia	0.27	1	0.603	0.00%
China	48	0.674	0.619	0.729	24.81	China	4584.31	47	0	99.00%
Fiji	2	0.162	0	0.329	1.76	Fiji	24.59	1	0	95.90%
French	27	1.261	1.131	1.391	9.53	French	9182.83	26	0	99.70%
Japan	18	0.572	0.469	0.675	7.88	Japan	2035.85	17	0	99.20%
Kiribati	14	3.904	2.982	4.825	3.24	Kiribati	28535.13	13	0	100.00%
Macaronesia	1	1.4	1.194	1.606	0.03	Macaronesia	0	0	.	.%
Mexico	1	0.15	0.111	0.189	0.64	Mexico	0	0	.	.%
NM[a]	4	0.003	0.009	0.051	7.92	NM	1379.47	3	0	100.00%
Portugal	16	0.011	0.01	0.013	31.33	Portugal	1940.5	15	0	99.20%
Spain	10	0.224	0.148	0.301	5.97	Spain	356.49	9	0	97.50%
UK	2	0.17	0.091	0.25	1.18	UK	6.11	1	0.013	83.60%
USA	8	0.463	0.327	0.6	3.28	USA	188.62	7	0	96.30%
Vietnam	1	1.88	1.402	2.358	0.01	Vietnam	0	0	.	.%
Overall	**154**	**0.195**	**0.191**	**0.198**	**100.00**	**Overall**	**1.0E + 05**	**153**	**0**	**99.90%**

[a] Not mentioned.

Vietnam (1.880 μg/kg) > Macaronesia (1.400 μg/kg) > French (1.261 μg/kg) > China (0.674 μg/kg) > Japan (0.572 μg/kg) > USA (0.463 μg/kg) > Spain (0.224 μg/kg) > UK (0.170 μg/kg) > Fiji (0.162 μg/kg) > Mexico (0.150 μg/kg) > Australia (0.138 μg/kg) >Portugal (0.011 μg/kg) (Table 1). As it is obvious from the results of this study, the CTXs concentrations vary between different countries and between different water resources. There are numerous factors including fish habitat, fish species, and the trophic level of fish, fish size, tissue, and the method used for CTXs determination affecting these variations which will discuss in the following, in detail.

Pacific and the Indian Ocean as well as the Caribbean Sea (where coral reef grown) are endemic areas for ciguatera disease [72]. Therefore, CTXs, based on their geographical distribution, are categorized as Pacific ciguatoxins (*P*-CTXs), Indian ciguatoxins (I-CTXs), and Caribbean ciguatoxins (*C*-CTXs). CTX1B is recognized as the most toxic CTX, among others [59,60,73–75]. Although there is no allowable level for CTX in fish, the United States Food and Drug Administration (US FDA) has recommended a regulation limit of 0.01 and 0.1 μg/kg for CTX1B and CTX1C, respectively. It is worth to mention that these limits were based on a 10-fold decline of the lowest level of CTXs in food leftovers reported to initiate human disease [76–79]. When it comes to countries, the results showed that the CTX concentration in all countries is higher than the safe limits of CTX1C (0.1 μg/kg). However, based on the safe limits of CTX1P, the concentrations of CTXs in just Portugal meet the regulation level (0.01 μg/kg).

Environmental and biological factors are the most important factors causing CFP [80]. Oshiro et al. (2021) observed considerable variations in the CTXs structure in fish of different species and harvested from various areas [62]. The ciguateric fish are normally distributed between 35 N and 35 S (ciguatera belt or hot spots) [61]. In these regions, the occurrence of CTXs is discrete, diverse, and site-specific [74]. There is new evidence that toxic fish are happening at greater latitudes due to climate change [81]. They are mostly endemic to tropical areas such as the South Pacific, the Indian Ocean, and the Caribbean Sea. However, global warming and the increasing global trade of tropical fish species in addition to the absence of reliable and practical analysis approaches for CTXs surveillance have resulted in raising the occurrence and proliferation of ciguateric fish in mild and temperate areas [74,82,83]. For instance, the incidences of Gambierdiscus in Macaronesia show that environmental alterations including global warming and its fundamental drivers, are quickly modified habitats [48]. Moreover, extreme abundance of nutrients in water bodies (regularly resulted from land runoff) could trigger a heavy increase of plant life like algae and subsequently abundance of ciguateric fish [84].

The sort of water resources based on the pooled concentration of CTXs was St Barthelemy (7.875 μg/kg) > Coral reef (4.732 μg/kg) > Marakei and Tarawa (2.081 μg/kg) > Nuku Hiva Island (1.692 μg/kg) > Amami and KakeromaI (1.675 μg/kg) > Okinawa (1.061 μg/kg) > Pacific (0.637 μg/kg) > Guadeloupe (0.516 μg/kg) > Fuerteventura (0.490 μg/kg) > Caribbean (0.489 μg/kg) > Hobcaw Creek (0.300 μg/kg) > Tenerife (0.244 μg/kg) > Virgin Islands (0.170 μg/kg) > Island of Hawai'i (0.170 μg/kg) > Viti Levu Island (0.162 μg/kg) > New South Wales (0.130 μg/kg) > Canary Islands (0.058 μg/kg) > Oceanic (0.017 μg/kg) > Selvagens Islands (0.011 μg/kg) (Table 2). Regarding water resources, the results showed that the CTXs concentration in all water resources is higher than the safe limits of CTX1C (0.1 μg/kg) and CTX1B (0.01 μg/kg). Consistent with our meta-analysis, several studies were conducted in different countries. For example, in Australia, Hamilton et al. indicated mean concentration of CTXs in 19 samples of Sawtooth barracuda was (0.140 μg/kg) [59]. In another study, in China, Kohli et al. concluded mean concentration of CTXs in 20 samples of Cheilinus undulates, Epinephelus fuscoguttatus and Epinephelus was (0.150, 0.223, and 0.200 μg/kg) [61]. In French, Oshiro et al. reported mean concentration of CTXs in 5 samples of Kyphosus cinerascens, Lethrinus olivaceus and *Liza vaigiensis* was (0.475, 0.553, and 16.23 μg/kg) [64]. Yogi et al. study showed mean concentration of CTXs in 5 samples of Lutjanus monostigm was (0.052 μg/kg) in Japan [85]. In Portugal, Costa et al. showed mean concentration of CTXs in 15 samples of Balistes capriscus was (0.030 μg/kg) [86]. In

Table 2
Meta analysis concentration of ciguatoxin in fish based on sampling location (μg/kg).

Sampling location	Number of studies	ES	Lower	Upper	Weight (%)	Heterogeneity statistic	Degrees of freedom	p value	I^2
Pacific	62	0.637	0.587	0.686	32.56	11920.35	61	0	99.50%
New South Wales	1	0.130	0.097	0.163	0.81	0	0	.	.%
Viti Levu Island	2	0.162	0.001	0.329	1.76	24.59	1	0	95.90%
Nuku Hiva Island	22	1.692	1.490	1.894	2.95	929.34	21	0	97.70%
Guadeloupe	5	0.516	0.372	0.661	6.58	2201.74	4	0	99.80%
Okinawa	6	1.061	0.689	1.434	0.95	418.71	5	0	98.80%
Amami and KakeromaI	4	1.675	0.734	2.616	0.84	147.74	3	0	98.00%
Coral reef	7	4.732	3.282	6.183	2.09	19171.96	6	0	100.00%
Marakei and Tarawa	6	2.081	1.632	2.530	1.14	620.68	5	0	99.20%
Caribbean	7	0.489	0.296	0.683	1.02	126.58	6	0	95.30%
Oceanic	4	0.017	0.013	0.021	7.92	1760.42	3	0	99.80%
St Barthelemy (Frenc	1	7.875	7.242	8.508	0.00	0	0	.	.%
Selvagens Islands	16	0.011	0.010	0.013	31.33	1940.5	15	0	99.20%
Canary Islands	5	0.058	0.030	0.086	3.75	9.1	4	0.059	56.00%
Tenerife	2	0.244	0.001	0.489	1.99	72.25	1	0	98.60%
Fuerteventura	1	0.490	0.417	0.563	0.23	0	0	.	.%
Virgin Islands	2	0.170	0.091	0.250	1.18	6.11	1	0.013	83.60%
Island of Hawai'i	1	0.170	0.164	0.176	2.48	0	0	.	.%
Hobcaw Creek	1	0.300	0.249	0.351	0.42	0	0	.	.%
Overall	**154**	**0.195**	**0.191**	**0.198**	**100.00**	**100000.00**	**155**	**0**	**99.90%**

Spain, Yogi et al. showed mean concentration of CTXs in 5 samples of Black moray eel (m. Helena), Common two-banded seabream, and Dusky grouper was (0.21, 0.17, and 0.59/kg) [27]. As it is well-known, the source of CTXs was identified mainly from the benthic dinoflagellate of genera Gambierdiscus [62]. Thus, the ciguateric fishes' distribution is related to toxic dinoflagellate (genus Gambierdiscus) populations [74]. In this regard, it is found that the presence of Gambierdiscus growth has a seasonal trend, in which the maximum densities occur during the warm seasons. Furthermore, the CFP risk is notably raised in vastly corrupted coral reef environments possibly due to anthropogenic discharges and the natural heat. Previous surveys have presented that biological processes and environmental factors including water temperature, water depth, alterations in the seasons, salinity, turbulence/flow rates (wave energy regime), and other habitat characteristics (like rainfall, light, and presence of carbonate banks) might have diverse effects on growth and distribution of different Gambierdiscus species which could influence the CTXs levels in fish [74,79,80,82,87]. Moreover, the species and size of Gambierdiscus are important in the quantity of CTXs in the fish [82]. Also, anthropogenic activities and regular perturbations (i.e. disturbances like hurricanes) in oceanic and sea waters, such as nutrient inserting, and habitat changes, may also influence the quantity and distribution of Gambierdiscus spp. and subsequently ciguatoxin fish [48,88]. Loeffler et al. (2018) reported that calmer locations result in elevated CTXs levels in fish, which could be attributed to changes in the benthic source and/or fish activities [87]. In this regard, it is found that lower wave energy (less turbid), higher temperatures, and normal seawater salinity are more suitable for the development and distribution of Gambierdiscus [79].

It is well-known that some regions like the reef of Marakei and Tarawa (in the Republic of Kiribati) have been introduced as high-risk areas regarding CFP, since 1978 [75,89]. This region is situated in the tropical area of the central Pacific Ocean [74,89]. It is revealed that Gambierdiscus spp. are the major benthic dinoflagellates in Marakei [89]. Moreover, Saint Barthelemy is enclosed by deep fringing reefs and most corals present there are recognized to be at high risk due to favorable situation for Gambierdiscus spp. colonization [65]. However, the measurement of Gambierdiscus spp. communities, to recognize ciguatera-endemic regions, is not always correct [74]. For example, while CTX-generating microalgae have been found in the Mediterranean Sea, no CTXs has been revealed in fish [48]. Furthermore, the factors that affected the biogeographic growth of toxic Gambierdiscus species in regions like the Canary Islands and Portugal are yet unknown [90]. In the case of the Canary Islands, the authorized control rules executed by the Canary Government, prevent toxic fish from being distributed to the market [47]. Therefore, this area was known a non-endemic area for CFP [88].

Other factors influencing the concentration of CTXs in fish are included the amount of food intake, the presence of CTXs and their precursors in fish diet, the trophic level, the size, the genera/species of fish, the efficiency of CTXs absorption, the rate of biotransformation of CTXs and its precursors, the efficiency of CTXs excretion and the rate of fish growth [91,92].

CTXs accumulates in the body of different fish species through the food (trophic) chain, and with different structural changes along this chain, about 20 different types of this toxin are created [84]. CTXs, generated by the benthic microalgae (dinofagellate Gambierdiscus toxicus), are consumed by herbivorous fishes and then passed on within the sea food chain to attain the larger carnivores [63,65,72,88,93]. It is reported that the CTXs' structure are different between herbivorous and omnivorous fishes [89]. CTXs appearance is a time-dependent phenomenon and is found first in herbivores (lower trophic level feeding on macro algae and microalgae; like surgeonfish and parrotfish) and in omnivorous (like Diplodus cervinus and Bodianus scrofa) and last in carnivorous fish (higher trophic level feeding on small herbivores) like moray eels (Lycodontis javanicus), grouper (Epinephelus marginatus) and red snapper (*Lutjanus bohar*) [77,89,91,94]. It is also reported that CTXs are often existed in large reef fish (top predators) such as dusky grouper (Epinephelus marginatus), barracuda (*Sphyraena barracuda*), amberjack (Seriola dumerili), and jack (Caranx spp.) [86,90]. In this regard, less oxidized and more oxidized (more poisonous) forms of CTXs are found in fish of lower and higher trophic levels (predators), respectively [61,91]. Furthermore, with increasing the trophic level, the profile of CTXs structure changes, due to the existence of higher CTXs contents in the diet of higher trophic level fishes (carnivorous), greater bioaccumulation capacity of CTXs in carnivorous fishes, and higher potential of carnivorous fishes to biotransform of CTXs [74,89]. It is worth mentioning that there are significant interspecific differences in CTXs types and concentrations in fish at different trophic levels, due to different abilities for CTXs accumulation in different fish species [94]. Moreover, it is revealed that the elimination of CTXs in carnivorous fish, like moray eels and red snapper is slow [94].

As previously mentioned, the accumulation level and type of CTXs in fishes is depended on their food resources [91]. Herbivorous fish, like Trochus. niloticus, surgeonfish (genus Acanthurus) and genus Naso feed mostly on algae (filamentous and leafy) and biofilm located on the corals and rocks and are simultaneously able to bioaccumulate CTXs in their tissues [80,89]. Moreover, mullet feeds mostly on debris, *vis.* organic materials and pelagic microalgae [91]. Carnivorous fish such as grouper, snapper, wrasse, and moray eel (*Muraena helena*) mainly feed on smaller fish and to less amount on crustaceans, holothurians, and cephalopods [89]. Although porcupinefish (black-blotched and spot-fin) are top predators, but their CTXs levels are extremely lower than those found in groupers and snappers, due to their feeding favorites which the former feed mainly on mollusks, crustaceans, and sea urchins, whereas the latter groups feed mainly on other fish [89].

Higher than 400 fish species are reported as vectors of CTXs. Groupers, snappers, mackerels, amberjacks, triggerfish and surgeonfish are the main groups of fish with higher CTXs accumulation rates [48,74]. Several researches have indicated that omnivorous and carnivorous fish are the largest part of ciguateric species [48,74]. However, some researchers noted that some herbivorous fish contain higher levels of CTXs compared to omnivorous and carnivorous. Clausing et al. (2018) reported that there is no or weak relationship between CTXs levels and trophic levels in fish, based on the CTXs congeners. Clausing et al. (2018) reported that algal large quantities on the reef are not simply connected with the possibility of CTX accumulation [95]. Moreover, in a study done by Darius et al. (2007) in Nuku Hiva was found that herbivores fish have the higher CTXs level in comparison to carnivorous fish, probably due to the accumulation and concentration of CTXs in lower trophic levels [64]. Soliño and Costa (2020) studied different fish in Marakei and analyzed for CTXs analogues (CTX1B and CTX-2 and 3) and their results showed a weak relationship between trophic level and CTX1B level. Furthermore, CTXs were detected in 76, 72, and 54% of carnivorous, omnivorous and herbivorous fishes, respectively. The prevailing CTX type in herbivorous and piscivorous fish (carnivorous and omnivorous) was CTX-2 and CTX1B, respectively [48]. The reason for this observation could attribute to high structural variability in Gambierdiscus existence, interactions with reef trophic levels, and fish behavior (like migration and home choices). The degree of absorption, metabolization and elimination of CTXs play an important role in CTX concentration in the fish body, which is species-, trophic level-and site (habitat)-specific [95]. Moreover, given the migratory behavior of fish, the CTXs concentrations could vary related to the catch location [85].

Previous researches has shown a positive relationship between size (weight and length) and CTXs content in some fish species [65,72,79,87,89]. Since CTXs can accumulate over time, therefore larger and older fish have probably higher content of CTXs [60]. Furthermore, consuming larger prey by larger fish could subsequently increase CTXs accumulation in their body [79]. Thus, it was recommended that fish with weight lower than 1 kg may decrease the risk of CFP [61] and larger fish (within the same species) are more hazardous [48,65]. It is worthwhile to mention that only a small number of fish species (like *Lutjanus bohar*) showed a positive correlation between size and CTXs concentration [48,60,65]. In addition to age, biological and behavioral differences (diet, trophic level, species) between fish, the habitat (location) properties and anthropogenic activities also affect the size and toxin concentration in the fish [79,95]. When it comes to biological properties, it is noteworthy that the type of fish diet changes with age. For instance, young lionfish feed mainly on crustaceans and mollusks, while older ones feed mainly on teleost fish [65] which could result in differences in CTXs bioaccumulation. Regarding fish habitat, it is worth noting that a better supply for fish growth in some location could result in larger fish. Moreover, reducing fishing pressures due to the fear of collecting poisonous fish, result in prevailing larger and older fish communities containing more toxin level [79]. As fisheries are forbidden, fish could grow up and achieve a larger size and live longer which results in gradually more accumulation potential of CTXs [83]. However, several previous studies have reported that there is no or even negative correlation between size and CTX's concentration in the fish [48,81]. To justify this observation, it can be said that continuous accumulation of CTXs in a fish could be hidden by physical growth during its life (dilution of toxin with weight gain) [79]. Therefore, it is not always true to believe that smaller fish are less toxic and safer for human consumption [79] while, as previously noted, this relationship is species- and regional-specific [60].

During CTXs movement within the food net, it is metabolized to produce more than 20 diverse congeners. This toxin and its metabolites are distributed differently in tissues, with an order of extent lower in the muscle than in the viscera (especially in the liver) [96]. However, it is worth noting that toxin concentration in different tissues differs among different species, representing that toxins are accumulated in various fish species, differently. For example, CTXs stores in the liver of moray eels more than 100 times compared to those found in the muscle, while this amount is more than 10 times in groupers and great amberjack. However, in the mackerels this amount is the lowest among others [48]. Oshiro et al. (2021) also ranked the CTXs concentrations from low to high in the following order: muscle, brain, skin, gill, intestine, and liver [73]. It should bear in mind that CTXs concentration is tissue- and fish species-specific. The results of Ramos-Sosa et al. (2022) study depicted that in almost all of the fish species, except amberjacks, the flesh is less toxic than the liver. The reason for this observation is obvious as the liver is the first organ subjected to any substance ingested and is responsible for the metabolism of all toxins via cytochrome p450 enzymes. However, the muscle needs more time for CTXs accumulation. Therefore, it is suggested that the muscle could consider as an objective tissue for storage of CTXs, while the liver act as an indicator of recent CTXs exposure [47].

Until now, there are no official techniques for the detection of CTXs [65]. However, there are different methods used for detection and measurement of CTXs in fish including biological assays (like mouse bioassay (MBA)), chromatographic methods (like HPLC, UPLC or LC), immunological methods (like ELISA), pharmacological techniques (like receptor binding assay (RBA)), cytotoxicity assays and the reporter gene assay [64,97,98]. Each technique has its own merits and demerits [76]. Differences in method sensitivity and accuracy in addition to existence of different CTXs congeners are some factors affecting CTXs concentration in the same fish sample [72].

4. Conclusion

This study was conducted with the aim of meta-analysis of CTXs concentration in filled fish based on countries and water source subgroups. The concentration of CTXs in filled fish was highest in Kiribati, Vietnam and Macaronesia countries. Also, CTXs concentration was the highest in St Barthelemy, Coral reef, Marakei and Tarawa water sources. The concentration of CTXs in many countries and water sources were found to be higher than the permissible limits, which indicates the need to carry out control programs to reduce the concentration of CTXs in fillet of fish. Considering the increase in the prevalence of allergic symptoms caused by eating seafood in many countries, it is recommended to conduct a study on the association between CTXs concentration and the prevalence of allergic symptoms in consumers. On the other hand, in many countries, no studies have been conducted on the concentration of CTXs in fish, and it is recommended to carry out these studies for a better interpretation of the prevalence and concentration of CTXs in the world.

Consent to participate

The authors declare their Consent to Participate in this article.

Consent to publish

The authors declare their consent to publish this article.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18500.

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