



Tetracycline residues in tilapia and catfish tissue and the effect of different cooking methods on oxytetracycline and doxycycline residues

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Abstract

Fish such as tilapia (*Oreochromis niloticus*) and catfish (*Clarias gariepinus*) is an important source of high biological value animal protein. Fish can be exposed to antimicrobials in intensive aquaculture systems or exposed to remnants of the antimicrobials released to various water bodies via drainage systems. This study aimed at screening for antimicrobial residues in two major fish species commonly consumed in Egypt, namely, tilapia, and catfish, either in wild or cultured fish using a microbial inhibition assay. Besides, quantitative estimation of tetracycline (oxytetracycline and doxycycline) residues in the edible fish muscles was carried out using the solid phase extraction (SPE) technique and high-performance liquid chromatography with photodiode-array detection (HPLC-PAD). In addition, the effects of different cooking methods (pan-frying, grilling, and microwaving) on oxytetracycline and doxycycline residues in tilapia and catfish were investigated. The microbiological inhibition assay revealed that 2, 24, 18, and 32% of the examined wild tilapia, cultured tilapia, wild catfish, and cultured catfish, respectively, contained antibiotic residues. Cultured tilapia, wild catfish, and cultured catfish had mean concentrations of oxytetracycline residues of 0.147 ± 0.067 , 0.106 ± 0.046 , and 0.313 ± 0.044 $\mu\text{g/g}$. 3 (6%), 4 (8%), and 9 (18%) of the sampled cultured tilapia, wild catfish, and cultured catfish exceeded the established maximum permissible limits (MPL) of tetracycline (0.100 ng/g). The mean concentrations of doxycycline residues were 0.276 ± 0.045 , 0.026 ± 0.004 , and 0.070 ± 0.010 $\mu\text{g/g}$ in cultured tilapia, wild catfish, and cultured catfish, respectively, with 2 (4%) of the cultured tilapia exceeding the MPL of doxycycline. Consumption of fish with high residual levels of tetracyclines might pose potential health risks to consumers. In an experimental trial, heat treatment of tilapia and catfish could significantly reduce both oxytetracycline and doxycycline residues, particularly grilling had the highest reduction rates.

Keywords Fish · Antibiotic residues · Heat treatment · Oxytetracycline · Doxycycline

1 Introduction

Fish, including tilapia (*Oreochromis niloticus*) and catfish (*Clarias gariepinus*) provides humans with high biological value proteins, essential fatty acids, minerals such as calcium, and phosphorus, and vitamins such as Vitamins E and D (Javaheri Baboli and Velayatzadeh 2013; Morshdy et al. 2021). Nile tilapia and the North African catfish are among the most dominant cultured fish species in Egypt. Tilapia represented about 60% of the total cultured fish in Egypt in 2018 with 1,051,444 tons; while the production of catfish is limited to 6,836 tons (FAO 2020; Kaleem and Sabi 2021).

During the intensive fish farming, bacterial diseases are considered as the most vital problems facing this culture system in aquaculture industry in Egypt (Abdel-Rahman et al. 2020).

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Therefore, antimicrobials are used at uncontrolled levels for the purpose of prevention and control of such bacterial diseases, or as feed additives to enhance fish growth. However, the abuse and non-observance of the withdrawal times of such antimicrobials might lead to the occurrence of drug residues in the edible tissue of fish. Humans could be exposed to such residues via consumption of contaminated tissues (Morshdy et al. 2013; Thompson and Darwish 2019).

It has been well documented that long-term consumption of animal products containing high levels of antibiotic residues causes allergic reactions in some hypersensitive individuals and, more broadly, antibiotic resistance in humans (Liu et al. 2013). Furthermore, toxicological implications such as mutagenesis, teratogenesis, and carcinogenesis are also regarded as potential adverse effects of consumption of foods with antimicrobial residues (Baynes et al. 2016; El-Ghareeb et al. 2019). However, monitoring of antimicrobial residues in aquaculture has received little attention.

Tetracyclines are large group of broad-spectrum antibiotics that include oxytetracycline and doxycycline. Tetracyclines are widely available because of their cheap price and efficacy in the treatment of several infectious diseases. Oxytetracyclines are considered the most prescribed antibiotics in many of the African countries including Egypt (Darwish et al. 2013; Alsayegh et al. 2021).

In some parts of the world like far east, fish is consumed raw. However, in Egypt, fish is firstly heat-treated by different methods including either pan-frying, grilling, or microwaving (Morshdy et al. 2019). On the other hand, the effects of various cooking methods on tetracycline residues in fish are less well understood.

In sight of the previous facts, this study aimed to estimate tetracycline (oxytetracycline and doxycycline) residues in Nile tilapia and North African catfish either wild or cultured and retailed in Egypt. Furthermore, the effects of different cooking methods (pan-frying, grilling, and microwaving) on tetracycline (oxytetracycline and doxycycline) residues in tilapia and catfish were investigated in an experimental trial. The public health significance of the occurrence of antimicrobial residues in fish was further discussed.

2 Material and methods

All experiments using animals were conducted according to the guidelines of Zagazig University, Egypt.

2.1 Collection of samples

A total of two hundred fish samples (100 each of tilapia and catfish) were collected according to the simple random sampling method. The number of samples was determined based on a confidence level of 90%, and a margin of error of

10%. Samples were collected from cultured fish retailed in fish markets, and wild fish directly after catching by fishermen (50 each for each fish species). Cultured tilapia had an average body weight of 205 ± 20 g, while wild tilapia had an average body weight of 140 ± 25 g. Cultured catfish had an average body weight of 440 ± 75 g, while wild catfish had an average body weight of 380 ± 60 g. Both cultured Nile tilapia, and catfish were collected from different aquacultures with different conditions in Sharkia Governorate, Egypt. Wild fish samples were bought directly after catching by fishermen from Bahr Moise (a branch from River Nile) running in Sharkia Governorate, Egypt. Samples were collected during the period of January to June 2021. Samples were transferred in a cooled ice box to the laboratory for screening for antimicrobials without any delay.

2.2 Screening for antimicrobial residues using a microbial inhibition assay

A microbial inhibition assay was employed for the purpose of screening for antimicrobial residues in the examined fish muscles (Koenen-Dierick et al. 1995) with some modifications (Kilinic et al. 2007). 10 g from the back muscles of each fish were homogenized in 10 ml of phosphate buffer saline (pH 7.0) to make a muscle/buffer suspension. The tester organism was *Bacillus subtilis* BGA strain. Mueller–Hinton agar plates were prepared at pH 7.0. Wells were drilled in the agar plates using a sterile 8 mm diameter cork-borer for introduction of the examined samples. 1 ml of fish muscle/buffer suspension was introduced into such wells, followed by incubation of the agar plates at 37 °C for 24 h. After incubation, observation of a zone of inhibition of 1 cm or more was considered a positive case of fish muscle sample containing antimicrobial residues.

2.3 Quantitative analysis of tetracycline residues in fish muscle samples

2.3.1 Sample extraction

The method of Jevinova et al. (2003) was used for sample extraction, detection, and quantitation. In brief, a mixture consisting of 2 ml of the sample homogenate, 1 ml nitric acid (30%), 0.1 ml citric acid, 4 ml methanol, and 1 ml of deionized water was prepared and kept at ultrasonic bath for 15 min, followed by centrifugation at 5300 rpm for 10 min, and filtration through a 0.45 µm nylon filter. Then, 20 µl of the solution was injected into the HPLC system (a constant liquid chromatography pump provided with an auto sampler plus surveyor, ThermoScientific Company, USA) for analysis.

2.3.2 Chromatographic conditions

A mobile phase of methanol and formic acid 0.1% using a gradient method with a flow rate of 1.5 ml/min at 25 °C was used. The separation was done on hypersil gold C18 (10 µm, 100×4.6 mm) column with mobile phase. Detection was performed with a photodiode array (PDA) detector set at 350 nm wavelength. Quantification of residues in samples was obtained and calculated from areas under curves extrapolated automatically by the software Chromo Quest 5.

2.3.3 Calibration curves

Calibration curves for oxytetracycline and doxycycline were prepared by using concentrations of 0.05, 0.1, 0.2, 0.5, 1.0, and 2.0 µg/g of oxytetracycline and 0.01, 0.05, 0.1, 0.3, 0.5, and 1.0 µg/g of doxycycline in the eluent. The detection limits for oxytetracycline and doxycycline were 0.05 and 0.01 µg/g, respectively, while the retention time was 3.5 and 3.6 min for oxytetracycline and doxycycline, respectively. The method was validated to be used in the fish matrix with recovery rates of 88, and 92% for oxytetracycline and doxycycline, respectively.

2.4 An experimental trial for studying the effect of heat treatment on oxytetracycline and doxycycline residues in fish muscles

In order to investigate the effect of heat treatment on oxytetracycline and doxycycline residues in the fish muscles, an experimental trial using both Nile tilapia and catfish was conducted. In brief, cultured Nile tilapia, and catfish (150 days old) were obtained from the fish farm at the Faculty of Veterinary Medicine, Zagazig University, Egypt, and divided into 4 groups as follows:

- group 1: Nile tilapia (n = 20) receiving oxytetracycline,
- group 2: Nile tilapia (n = 20) receiving doxycycline,
- group 3: catfish (n = 20) receiving oxytetracycline,
- group 4: catfish (n = 20) receiving doxycycline.

Fish received a basal diet with oxytetracycline or doxycycline supplementation at a dosage of 100 mg kg⁻¹ (Islam et al. 2015). The fish of all groups were fed 5% from the total biomass regularly 3× daily for 7 days (Soltan et al. 2013). After harvest, oxytetracycline and doxycycline were initially quantified in each fish as mentioned before. Then each fish group was subdivided into four subgroups (n = 5/subgroup, fish samples were selected randomly, where antimicrobial concentrations did not show any significant differences among raw samples and were within narrow ranges) (p > 0.05 when statistical analysis was done between each previously assigned four subgroups using analysis of

variance [ANOVA] followed by Tukey's HSD post-hoc test). Fish subgroups were assigned as:

- subgroup 1: control (raw fish without any heat treatment),
- subgroup 2: exposed to deep pan-frying in corn oil until browning of the fish muscle (at 190 °C for 10 min),
- subgroup 3: exposed to electric grilling at a temperature of 180 °C for 10 min on each side, and
- subgroup 4: exposed to microwaving at 1000-W voltage for 5 min.

The internal temperature of the fish muscle in all methods ranged between 63 and 65 °C (Morshdy et al. 2019). Fish muscles were collected after heat treatment and exposed to a final quantification of oxytetracycline and doxycycline residues as mentioned before.

2.5 Statistical analysis

ANOVA followed by Tukey–Kramer honestly post-hoc test (JMP program, SAS Institute, Cary, NC, USA) was used for statistical analysis with a p < 0.05 considered as significant.

3 Results

The microbiological inhibition assay revealed that 1/50 (2%), 12/50 (24%), 9/50 (18%), and 16/50 (32%) of the examined wild tilapia, cultured tilapia, wild catfish, and cultured catfish, respectively, contained antibiotic residues (Fig. 1). The results in Table 1 showed that oxytetracycline residues were detected in 5 (10%), 6 (12%), and 9 (18%) of the collected cultured tilapia, wild catfish, and cultured catfish, respectively, with mean values of 0.147 ± 0.067, 0.106 ± 0.046, and 0.313 ± 0.044 µg/g in the same species, respectively.

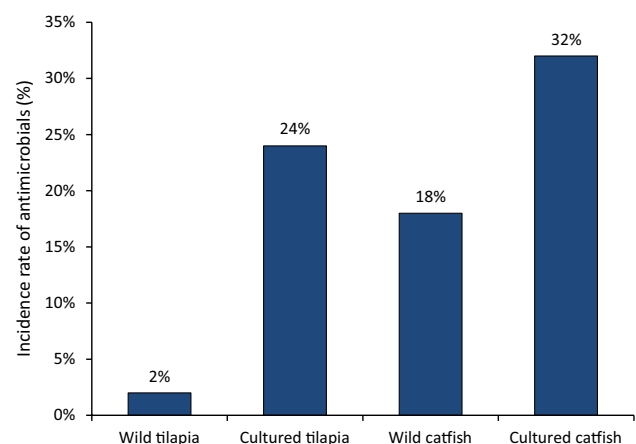


Fig. 1 Incidence of antibiotic residues (microbiological inhibition assay) in the muscles of the examined fish species (n = 50 for each)

Table 1 Oxytetracycline and doxycycline residues ($\mu\text{g/g}$) in the muscles of the examined fish species

Species	Oxytetracycline			Doxycycline		
	Incidence	Min–max Mean \pm SE	Samples higher than MPL (%)	Incidence	Min–max Mean \pm SE	Samples higher than MPL (%)
Wild tilapia	ND	ND	0	ND	ND	0
Cultured tilapia	5 (10%)	0.074–0.298 0.147 \pm 0.067 ^b	3 (6%)	3 (6%)	0.021–0.380 0.276 \pm 0.045 ^b	2 (4%)
Wild catfish	6 (12%)	0.025–0.214 0.106 \pm 0.046 ^b	4 (8%)	4 (8%)	0.014–0.036 0.026 \pm 0.004 ^b	0
Cultured catfish	9 (18%)	0.145–0.429 0.313 \pm 0.044 ^a	9 (18%)	6 (12%)	0.024–0.094 0.070 \pm 0.010 ^a	0

Means in the same column bearing different superscript letters are significantly different ($p < 0.05$). MPL refers to the maximum permissible limits of tetracyclines in fish (0.100 $\mu\text{g/g}$)

ND not detected

Furthermore, doxycycline was detected in 3 (6%), 4 (8%), and 6 (12%) of the collected cultured tilapia, wild catfish, and cultured catfish, respectively, with mean values of 0.276 ± 0.045 , 0.026 ± 0.004 and 0.070 ± 0.010 $\mu\text{g/g}$ in the same species, respectively. Neither oxytetracycline nor doxycycline were detected in wild tilapia. The highest oxytetracycline and doxycycline residues among the examined species was found in cultured catfish ($p < 0.05$). Comparing the detected levels of oxytetracycline and doxycycline residues in fish muscles with the established MPL of tetracycline (0.100 $\mu\text{g/g}$) revealed that 3 (6%), 4 (8%), and 9 (18%) of the sampled cultured tilapia, wild catfish, and cultured catfish exceeded MPL of oxytetracycline, while 2 (4%) of cultured tilapia exceeded MPL of doxycycline.

In an experimental trial, tilapia, and catfish were exposed to oxytetracycline and doxycycline for one week, then the exposed fish species were harvested one day after the last drug administration. The two fish species of each treatment were assigned into four groups: one acted as a control, while the other three for each species were

exposed to common cooking methods in Egypt. The levels of the tested antimicrobials did not show significant differences ($p > 0.05$) among the fish populations in each experiment before heat treatment, and the residual levels of the tested antimicrobials were within narrow ranges (Table 2). In tilapia, pan-frying, microwaving, and grilling reduced oxytetracycline residues to 89.56, 92.83, and 45.66%, respectively. Similarly, doxycycline residues were reduced to 35.89, 70.77, and 65.98% upon pan-frying, microwaving, and grilling, respectively (Table 2; Fig. 2). In catfish, oxytetracycline residues were reduced to 84.17, 89.62, and 75.38% after pan-frying, microwaving, and grilling, respectively, while doxycycline residues were reduced to 67.52, 78.99, and 58.64% upon pan-frying, microwaving, and grilling, respectively (Table 2; Fig. 3). Statistical analysis for the reduction trials revealed that grilling had the most significant ($p < 0.05$) reduction effects on oxytetracycline residues in both tilapia, and catfish. While all heat treatment methods significantly ($p < 0.05$) reduced doxycycline residues.

Table 2 Oxytetracycline and doxycycline residues ($\mu\text{g/g}$) in the muscles of the experimental groups of Nile tilapia and catfish after being heat-treated or not

	Nile tilapia		Catfish	
	Oxytetracycline	Doxycycline	Oxytetracycline	Doxycycline
	Range	Range	Range	Range
	Mean \pm SE	Mean \pm SE	Mean \pm SE	Mean \pm SE
Raw	1.077–1.285 1.173 \pm 0.060 ^a	0.197–0.220 0.208 \pm 0.006 ^a	1.416–1.516 1.463 \pm 0.028 ^a	0.513–0.547 0.533 \pm 0.010 ^a
Pan-frying	0.998–1.119 1.051 \pm 0.035 ^a	0.048–0.089 0.075 \pm 0.013 ^b	1.199–1.276 1.231 \pm 0.023 ^{ab}	0.257–0.438 0.360 \pm 0.053 ^{bc}
Microwaving	0.674–1.333 1.089 \pm 0.208 ^a	0.140–0.156 0.147 \pm 0.017 ^c	1.250–1.401 1.311 \pm 0.046 ^{ab}	0.346–0.463 0.421 \pm 0.037 ^{ab}
Grilling	0.447–0.606 0.535 \pm 0.046 ^b	0.139–0.157 0.148 \pm 0.004 ^c	1.036–1.189 1.103 \pm 0.045 ^b	0.249–0.378 0.313 \pm 0.037 ^c

Means in the same column bearing different superscript letters are significantly different ($p < 0.05$)

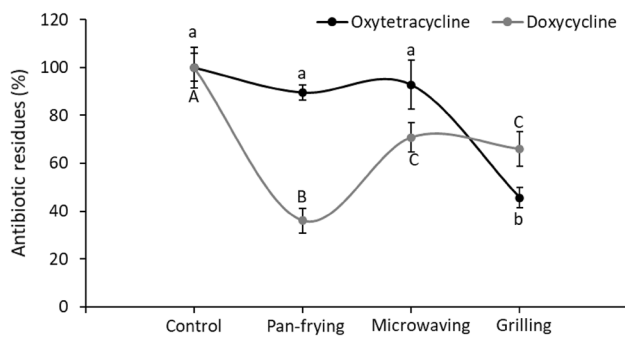


Fig. 2 Effect of different heat treatment on oxytetracycline and doxycycline residues in Nile tilapia. Symbols carrying different small letters (a, b) indicate statistically significant differences among different heat treatment methods on oxytetracycline residues. Symbols carrying different large letters (A, B, C) indicate statistically significant difference among different heat treatment methods on doxycycline residues ($n=5$ samples/treatment). Control indicates no heat treatment

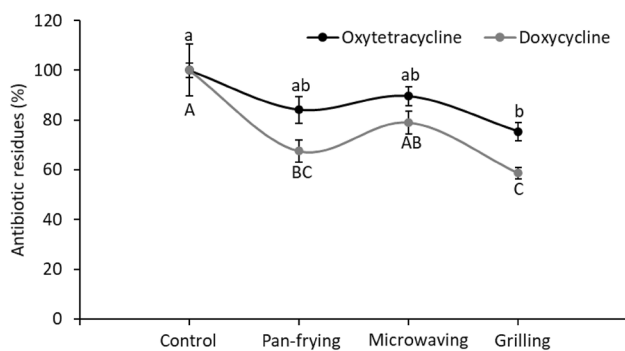


Fig. 3 Effect of different heat treatment on oxytetracycline and doxycycline residues in catfish. Symbols carrying different small letters (a, b) indicate statistically significant differences among different heat treatment methods on oxytetracycline residues. Symbols carrying different large letters (A, B, C) indicate statistically significant differences among different heat treatment methods on doxycycline residues ($n=5$ samples/treatment). Control indicates no heat treatment

4 Discussion

The first step in preventing antibiotic residues in animal-derived foods is to use screening procedures. Traditional screening methods rely on a variety of technologies, including microbiological, immunological, and physicochemical procedures (e.g., thin-layer chromatography, HPLC, and liquid chromatography tandem mass spectrometry [LC–MS/MS]). Simple, quick, cheap, and specific screening procedures with low detection limits and high sample throughput should be used (Gaudin 2017). In this context, a microbiological inhibition assay was firstly used in the present study. The obtained results were comparable to worldwide reports: in Spain 16/107 (14.95%)

of examined catfish (Hurtado de Mendoza et al. 2012), in Turkey 33.3% of examined sea bass, gilthead sea bream, and rainbow trout (Yipel et al. 2017) contained antibiotic residues. The detection of antibiotic residues in wild tilapia in the present study was very low (2%). This result agrees with the finding of Zhao et al. (2015) who examined the level of antibiotics in wild fish collected from China. The differences in the occurrence of antimicrobial residues in the present study and other reports might be due to the differences in the fish species, season of sampling, and assayed method. In comparison to farmed fish, wild fish might be accidentally exposed to antibiotics. Antibiotics could be consumed by wild fish through wash-down, animal excrements from husbandry farms entering the water body (Zhi et al. 2020). This could explain the very low level of antibiotic residues observed in the wild tilapia. Meanwhile, the high incidence of antibiotic residues in both wild and cultured catfish might be attributed to the habitat of the catfish as a bottom feeder, particularly in water bodies contaminated with animal and human effluent.

Tetracyclines were ranked the first among the used antibiotics in Africa (Darwish et al. 2013), possibly because of their wide spectrum, efficacy, and cheap price. Therefore, this study was extended to quantitatively estimate oxytetracycline and doxycycline residues using HPLC in the positive fish samples from the previous microbiological inhibition assay. Interestingly, wild tilapia was not contaminated with either oxytetracycline or doxycycline. Nearly similar concentrations of oxytetracycline were recorded in the cultured tilapia in Cairo, Giza, and Alexandria Governorates in Egypt (Abdel-Rahman et al. 2020). In contrast, oxytetracycline residues were detected at lower levels such as 0.004–0.092 $\mu\text{g/g}$ in fish collected from Spain (Cháfer-Pericás et al. 2010), 0.015 \pm 0.002 $\mu\text{g/g}$ in fish collected from South Korea (Kang et al. 2018), and 0.021 \pm 0.006 $\mu\text{g/g}$ in fish samples collected from Nigeria (Onipede et al. 2021). Higher oxytetracycline residues (0.553 $\mu\text{g/g}$) were detected in fish muscles collected from Nigeria (Olatoye and Basiru 2013). Among the possible reasons for the higher levels of tetracycline in some fish samples is the addition of tetracycline-containing materials, such as chicken manure, to aquaculture to increase the plankton, or the intentional addition of antimicrobials for the purpose of prevention and control of bacterial disease, and to enhance feed-conversion ratio (Aly and Albutti, 2014; Kaleem and Sabi, 2021). The European Union (EU 2010) set 0.100 $\mu\text{g/g}$ as the maximum residue limit (MRL) for oxytetracycline in fish muscles. As there is no national legislation related to antimicrobial residues in fish in Egypt, so the recorded concentrations in the fish in the current study were compared with European Commission guidelines. The acceptability of the examined fish samples

for oxytetracycline residues showed that 3, 4, and 9 samples of the examined cultured tilapia, wild catfish, and cultured catfish exceeded the established MRL. Doxycycline residues in this study match with the levels reported in the muscle of the grass carp ($0.049 \pm 0.005 \mu\text{g/g}$) collected from China (Xu et al. 2019). On contrary, doxycycline was not detected in fish collected from Greece (Dasenaki and Thomaidis 2010) and Nigeria (Onipede et al. 2021). All examined samples in this study were below the value of $0.100 \mu\text{g/g}$, the MPL of doxycycline established by EU (2010), except for two samples of cultured tilapia. Consumption of antimicrobial-contaminated fish might lead to several adverse health effects such as allergic reactions, development of drug-resistant pathogens, nephrotoxicity, hepatotoxicity, teratogenesis, mutagenesis, and cancer (Darwish et al. 2013). There was a clear lack of studies concerned with antimicrobial residues in fish. That could be attributed to the lack of awareness on the problem of antibiotic residues in aquaculture. Besides, in some places of the world, it appears that regulation prohibiting the misuse and uncontrolled usage of antimicrobial medications in fisheries, poultry, and animals is less strict (Li et al. 2017). In Egypt, strict legislations should be implemented to minimize the misuse of antibiotics in aquaculture, and to halt the marketing of antimicrobial-contaminated fish. Besides, risk management recommendations that recall the residual standards reported by the Codex Alimentarius (CX/MRL 2-2018) should be strictly followed (FAO/WHO/Codex Alimentarius 2018).

In an experimental trial, tilapia and catfish were exposed to oxytetracycline and doxycycline in their ration at prophylactic doses commonly used at their intensive rearing systems in aquaculture, and according to similar experimental trials (Islam et al. 2015; Soltan et al. 2013). The two fish species were harvested a day post administration and then exposed to different heat treatment methods including pan-frying, microwaving, and grilling. The obtained results indicated that doxycycline was much reduced in the two species with different cooking methods. The residues of the two tested antimicrobials were more reduced upon heat treatment in tilapia than in catfish. Interestingly, grilling had the highest reduction rates compared with other tested cooking methods, particularly on oxytetracycline in tilapia, and doxycycline in catfish. In agreement with the reported results of the present study, chloramphenicol was reduced by 6, 12, and 29% in shrimp cooked at 100°C for 10, 20, and 30 min, respectively (Shakila et al. 2006). Similarly, different cooking methods significantly reduced oxytetracycline residues in chicken (Hussein et al. 2016). In addition, heat treatment of tilapia and mullet could reduce their heavy metal load (Morshdy et al. 2019). Besides, Abdel-Rahman et al. (2020) reported significant reduction effects for frying and grilling on oxytetracycline residues in tilapia.

5 Conclusions

In conclusion, the obtained results of the present study revealed contamination of tilapia and catfish edible tissues with antibiotic residues, particularly with oxytetracycline and doxycycline. Several samples exceeded the recommended MPL of the tested antimicrobials, therefore consumption of such contaminated fish might pose potential health risks for consumers. In a reduction trial, efficient heat treatment of such contaminated fish muscles could significantly reduce the antimicrobial residues, particularly, grilling had the highest protective effects. Therefore, continuous monitoring studies of antimicrobial residues in aquaculture is highly recommended. Besides, efficient heat treatment of fish before serving to humans is highly advised.

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Declarations

Conflict of interest None.

Ethics approval and consent to participate This study was conducted according to the guidelines of Zagazig University, Egypt. All authors approved to participate in this research work and in the manuscript.

Consent for publication All authors approved this manuscript to be published.

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