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Quantification and Confirmation of Zearalenone Using a LC-MS/MS QTRAP System in Multiple Reaction Monitoring and Enhanced Product Ion Scan Modes

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Abstract

A simple, rapid, and efficient liquid chromatography tandem mass spectrometry (LC–MS/MS) method, operated in electrospray ionization (ESI) and quadrupole linear ion trap modes, has been developed for the identification and structural characterization of zearalenone (ZEN) in corn oil. Samples (5 g) were extracted with acetonitrile/water (80:20, v/v). After centrifugation and dilution, the extracts were separated on a C18 analytical column by gradient elution (acetonitrile/water) and analyzed by UPLC–MS/MS. The developed multiple reaction monitoring–information-dependent acquisition–enhanced product ion method enabled quantification and confirmation of the analyte in a single run. Enhanced product ion mode was used for qualitative analysis, while multiple reaction monitoring mode was used for quantitative analysis. An in-house library was constructed for identification. Calibration curve showed good linearity with correlation coefficients (r) higher than 0.995. Limit of detection was determined to be below 0.20 μg kg^{-1} for ZEN. The recovery for ZEN was in the acceptable range of 86.6 to 97.2%. 82.4 % of the samples were found to contain ZEN among the 51 samples.

Keywords Zearalenone · Multiple reaction monitoring (MRM) · Enhanced product ion (EPI) · Confirmatory method · Pollution level

Introduction

The mycotoxin zearalenone (ZEN) is a resorcylic acid lactone produced by several species of *Fusarium genus*, such as *Fusarium roseum*, *Fusarium tricinctum*, *Fusarium sporotrichioides*, *Fusarium oxysporum*, and *Fusarium moniliforme* (Metzler et al. 2010; Cavaliere et al. 2019; Lee 2019; Wang et al. 2015). In temperate and warm countries, these Fusarium species may colonize various cereal grains, such as maize, sorghum, wheat, barley, and oats (Paschoal et al. 2016; Rempelaki et al. 2015), mainly in the field but also post-harvesting under poor storage conditions (Wu et al. 2016; Li et al. 2015). Jiaxing, China, has a subtropical monsoon climate with highest temperatures in summer of 38–40 °C and humid and rainy weather, which is beneficial for breeding (Lv et al. 2019; Xu et al. 2019). Therefore, it is necessary to monitor ZEN levels in food in Jiaxing.

ZEN has shown to possess estrogenic activity due to its competitive binding to the estrogen receptor, which consequently disrupts the reproductive system and causes abnormal fetal development in animals (Bertero et al. 2018; Andrade et al. 2018). Besides the adverse hormonal effects, they have also been implicated in numerous mycotoxicosis of farm animals associated with hepatic and renal lesions in rodents and the reduction of milk production in cows (Dong et al. 2010; Han et al. 2017; Jiao-jiao et al. 2017). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has recommended a provisional maximum tolerable daily intake (PMTDI) of 0.5 μg kg^{-1}g for ZEN.

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Among cereals, corn stands out as a product with the highest rate and types of contamination (Paschoal et al. 2016; Beltrán et al. 2013; Bai et al. 2018). Also, corn is the main product of world agriculture and China is highlighted as the second largest producer of corn, behind the USA. Corn oil was extracted from corn germ. The corn oil was widely used in China, it is necessary to consider that the risk of ZEN in such products.

Most current methods for quantitative ZEN determination involve chromatographic methods, such as thin layer chromatography (TLC) and high-performance liquid chromatography (HPLC) (Majerus et al. 2009; Qian et al. 2015). Several immunology-based semiquantitative and qualitative methods, including enzyme-linked immunosorbent assays (ELISAs) and immunoaffinity column assays, have also been developed for use at grain stations and silos (Cavaliere et al. 2019; Wu et al. 2016; Sun et al. 2018). However, these methods are complex, inconvenient, and time consuming. Poor separation, unsatisfied accuracy, and low sensitivity limit the application of TLC. Although ELISA is a fast and sensitive method, false positive result might be obtained. Conventional approach by HPLC in a gradient reversed phase mode typically using columns with 5-μm particles often costs a lot of time to get a complete separation of the target compounds and, additionally, in order to improve the detection limit of ZEN a tedious pre- or post-column derivatization must be done. The extraction and purification steps for these methods involve liquid/liquid partition, solid phase extraction, or immunoaffinity chromatography. Each mycotoxin group is analyzed individually, which results in the significant use of time, human resources, and reagents and negative environmental impacts from the analytical residues. The present study will cope with this drawback using the ultra-high-performance liquid chromatography (UHPLC) method; the particle diameter of stationary phase reduced from 5 μm (HPLC) to sub-2 μm (UHPLC) results in increased speed, better chromatographic resolution, and improved sensitivity, selectivity, and specificity. The introduction of MS/MS detection also leads to a significant improvement for the analysis of ZEN because of its high sensitivity and ability to quantify ZEN without derivatization.

This study aimed to develop a liquid chromatography-coupled quadrupole tandem mass spectrometry (LC–MS/MS) method for the simultaneous quantification and detection of ZEN in corn oil in a single run. Structural characterization of the ZEN was performed using the information-dependent acquisition (IDA) method (Cao et al. 2017; He et al. 2018; Zeng et al. 2015; Zhou et al. 2018). The IDA method with dynamic background subtraction (DBS) was configured to trigger a sensitive enhanced product ion (EPI) scan when the survey scan signal exceeded the defined criteria (Attia et al. 2016; Lee et al. 2015; Xing et al. 2016). An EPI spectrum library was constructed and can be used for ZEN compound screening. This method should be stable enough to avoid false negative or false positive results.

Materials and Methods

Sample Collection and Storage

Between March 2017 and September 2019, 51 samples of corn oil were obtained randomly from markets, supermarkets, and local retailers in Jiaxing, China. The samples were transported to the laboratory in an insulated container and analyzed upon arrival.

Chemicals and Reagents

All standards and reagents used were of the highest purity commercially available. Reagent-grade water was obtained using a Milli-Q Ultrapure Water Purification System (Millipore, Bedford, MA, USA). HPLC-grade methanol and acetonitrile were purchased from Merck (Darmstadt, Germany). ZEN in acetonitrile (50 mg L^{-1}), was purchased from ANPEL Laboratory Technologies (Shanghai, China), and used to prepare calibration curves and recovery experiments. ^{13}C-ZEN in acetonitrile (25 μg mL^{-1}) was purchased from ROMER (Beijing, China).

Apparatus

The LC–MS/MS system consisted of a 30AD LC instrument (Shimadzu, Kyoto, Japan) coupled with a QTRAP5500 triple quadrupole mass spectrometer (AB SCIEX instruments, Foster, CA, USA). The LC-30AD system had two interconnected pump units, one with an integrated degasser and the other with a mixer, and was comprised of an UHPLC gradient system, a refrigerated autosampler, and a column oven compartment. A Waters BEH C18 column (100 mm × 2.1 mm, 1.7 μm) was used as the analytical column. The mass spectrometer was equipped with an electrospray ionization source and spectra were acquired in negative ion multiple reaction monitoring (MRM) mode and enhanced product ion (EPI) scan mode. Nitrogen was used as the nebulizer, heater, and curtain gas, and the collision-activated dissociation gas.

LC–MS/MS Conditions

The gradient elution solvent comprised acetonitrile (A) and water (B). The gradient was programmed as follows: 0–1 min, 95–80% B; 1–4 min, 80–75% B; 4–6 min, 75% B; 6–8 min, 75–0% B; 8–8.5 min, 0% B; 8.5–10 min, 0–95% B; and 10–12 min, 95% B. The column temperature was set at 40 °C, the flow rate was 0.3 mL min^{-1}, and the injection volume was 10 μL.

LC–MS/MS with electrospray ionization (ESI) was operated in negative mode. Tandem MS analyses were performed in MRM acquisition mode, with two precursor-to-product ion transitions monitored for simultaneous detection of all analytes. The optimized MS/MS parameters were as follows: Source temperature, 500 °C; ion spray voltage (IS), 5500 V; ion source gas 1 (GS1) pressure, 50 psi; ion source gas 2 (GS2) pressure, 50 psi; curtain gas (CUR) pressure, 20 psi; collision gas (CAD), medium. Table 1 shows the MRM parameters used in the optimized survey scan. The peak area of the most intense MRM transition was used for quantification.

In this study, an IDA (information-dependent acquisition) experiment was used to automatically trigger EPI scans by analyzing MRM signals. The EPI scans were operated in ESI^- mode for product ions at a scan rate of 10,000 Da/s, with dynamic fill in the linear ion trap and a step size of 0.12 Da. The collision energy (CE) spread of EPI was set at 40 eV, with a CE spread of 10 eV to provide rich EPI spectra. The CAD was set to high. The IDA criteria included selecting the most intense peak after dynamic background subtraction of the survey scan, for ions greater than m/z 50 and smaller than m/z 350 that exceeded 1000 counts per second (cps).

Calibration Curve of the IDA–MRM–EPI Method

The ZEN standard was used to prepare standard solutions by pipetting appropriate volumes into a set of 20-mL calibrated volumetric flasks and diluting with acetonitrile/H_2O (20:80, v/v) to volume. The ZEN concentrations were 0.05, 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, 10.0, and 20.0 ng mL^{-1}. ^{13}C-ZEN was diluting with acetonitrile to 0. 1 μg mL^{-1}. The internal standard ^{13}C-ZEN (0.1 μg mL^{-1}) 10 μL was added to each 990-μL ZEN standard concentration respectively.

Calibration curves were established using peak area ratio (ZEN/^{13}C-ZEN) as the dependent variable (*y*-axis) and the concentration of each analyte as the independent variable (*x*-axis). The linearity was evaluated from the correlation coefficient (*r*) value of each calibration curve. The LODs and LOQs for each analyte were calculated at signal-to-noise (S/N) ratios of 3 and 10, respectively, by analyzing several decreasing concentrations of each analyte until the relevant S/N ratio was reached.

Extraction

The sample preparation procedure was developed with reference to the method of Xu et al. (2016). The corn oil (5 g) was accurately weighed into a 50-mL centrifuge tube, and 60 μL ^{13}C-ZEN(1 μg mL^{-1}) was added, vortexing, sit for 5 min. Then 20-mL extraction solvent (acetonitrile/water, 80:20 (v/v)) was added. ZEN was extracted in a turbine mixer for 1 min, followed by vigorous vortexing for 30 min in an automatic vibrator. The extract was centrifuged for 5 min at 10,000 rpm and the resulting supernatant was collected. A 1-mL aliquot of the supernatant was transferred into a 5-mL centrifuge tube and diluted to 3 mL with water. The sample solution (1 mL) was transferred directly into vials for LC–MS/MS analysis.

Quality Assurance of the IDA–MRM–EPI Method

Specificity, Selectivity, and Accuracy

Corn oil samples were selected to evaluate the specificity and selectivity of this method. To verify the absence of interfering substances, the MRM chromatograms of the blank solvent, solutions of standard, and sample solutions were compared with regard to the retention time of the target analytes.

The accuracy and precision of the method were measured using the intra- and inter-day recoveries and RSDs. The standard solution of the ZEN was spiked into the corn oil samples to obtain spiked samples (three concentrations, 0.6, 6, 60 μg kg^{-1}). All spiked samples were detected three times a day on five different days.

Results

Specificity and Selectivity of the IDA–MRM–EPI Method

The total ion chromatograms (TICs) of blank solution and ZEN standard are shown in Figs. 1 and 2. TIC chromatograms of one positive corn oil sample are shown in Fig. 3,

Table 1 Retention time and MRM parameters of ZEN

Analytes	Retention time (min)	Precursor ions (m/z)	Product ions (m/z)	DP (v)	CE (v)
ZEN	7.48	317.1	175.1/131.1*	170	24/30
^{13}C-ZEN	7.48	335.1	185.1	170	26

*Quantitative ion

MRM Multiple reaction monitoring

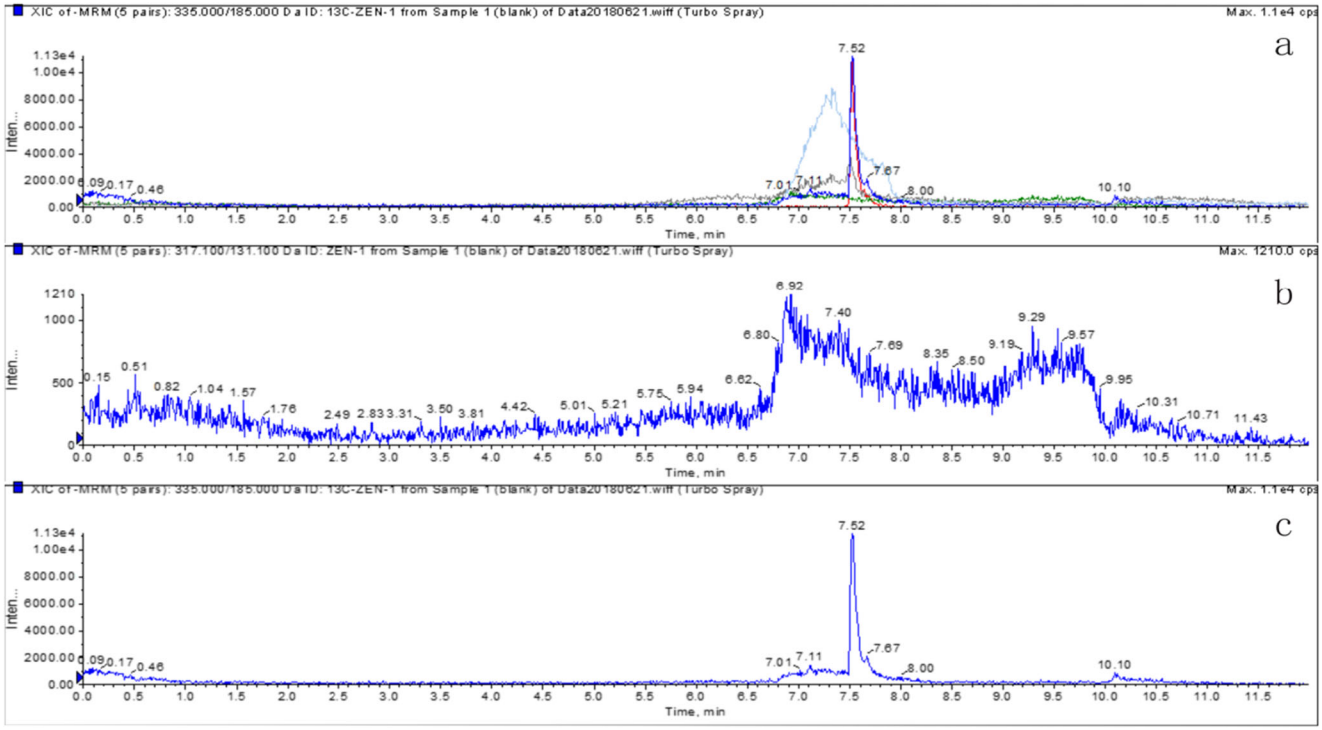

Fig. 1 TIC and XICs of blank solution. TIC, total ion chromatogram; XICs, extracted ion chromatograms. **a** TIC chromatogram. **b** XIC of MRM 317.1/131.1 Da ZEN. **c** XIC of MRM 335.0/185.0 Da 13C-ZEN

and no interference peaks from other constituents were observed at the retention time of the analyte for ZEN (7.48 min). Furthermore, the response of the analyte in the MRM chromatogram was high enough for quantification, demonstrating the high specificity and good sensitivity of the method.

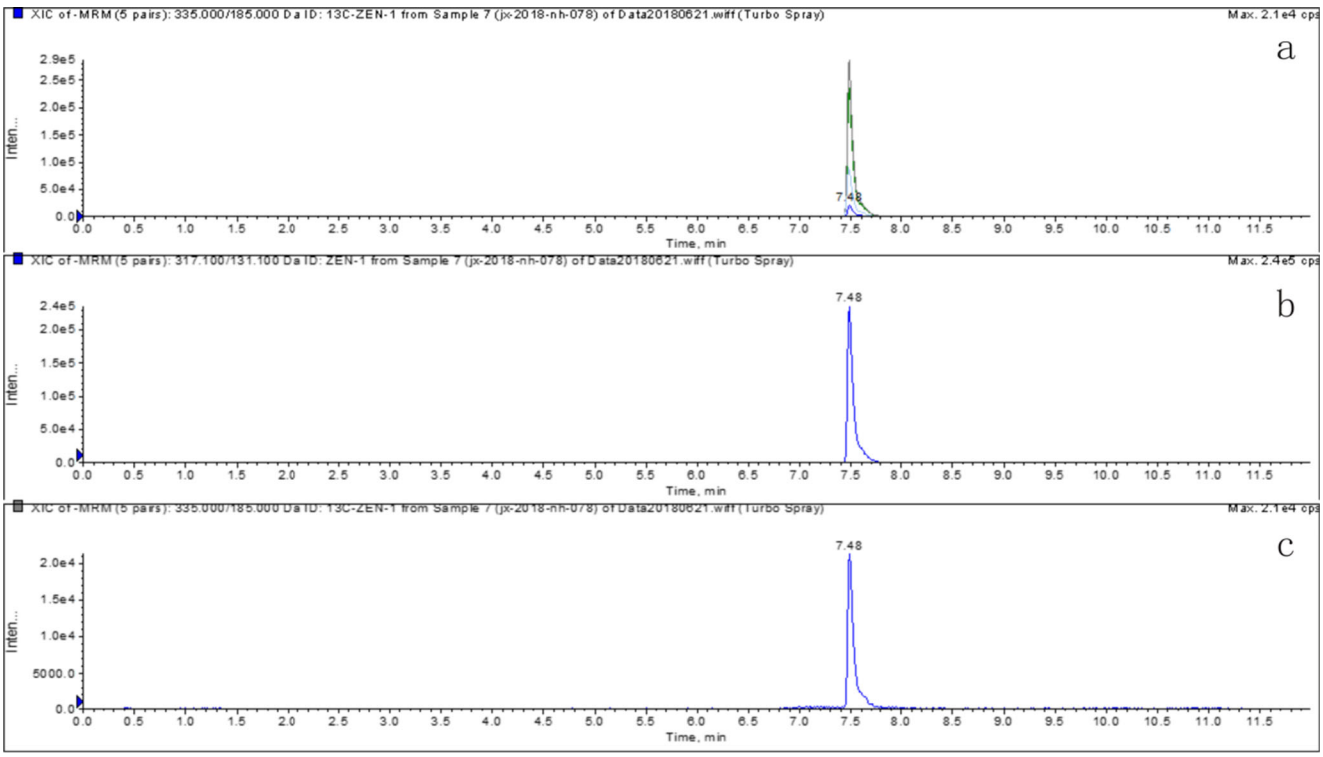

Fig. 2 TIC and XICs of standard solution. **a** TIC chromatogram. **b** XIC of MRM 317.1/131.1 Da ZEN. **c** XIC of MRM 335.0/185.0 Da 13C-ZEN

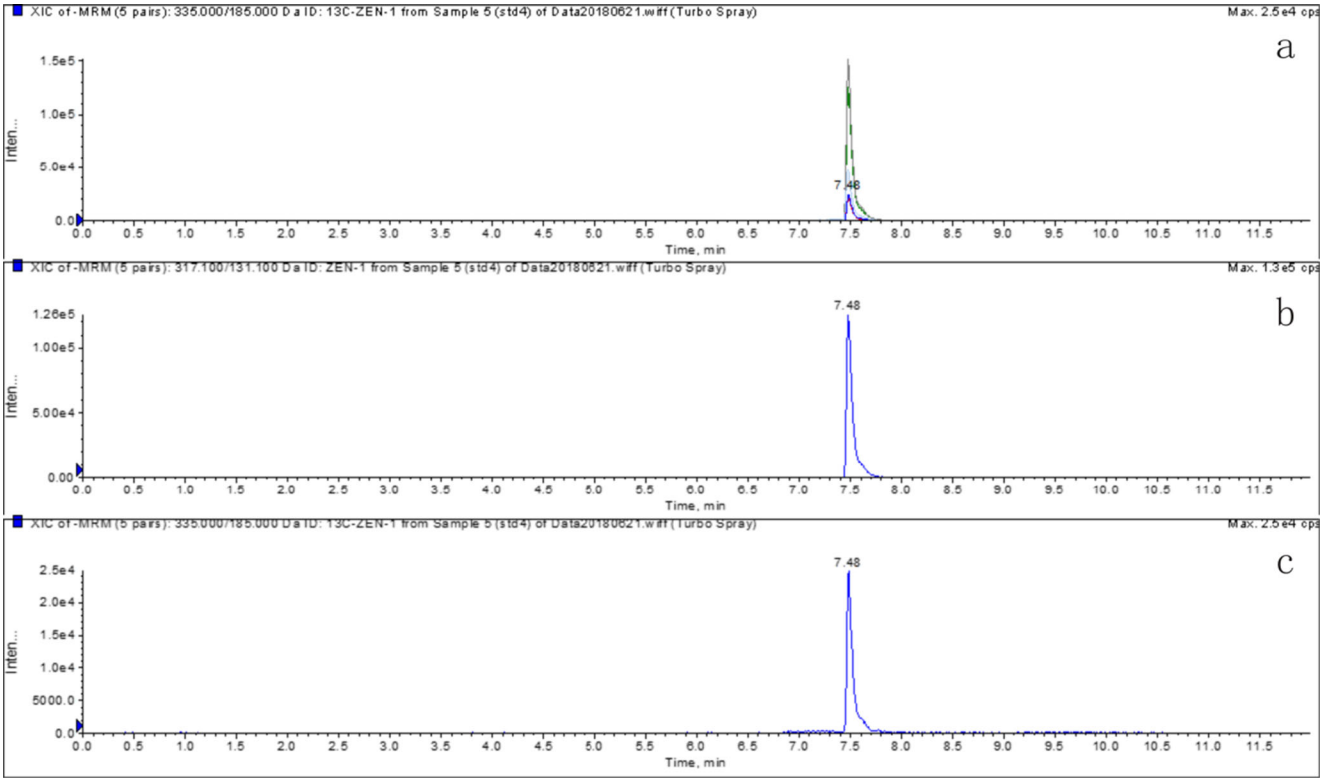

Fig. 3 TIC and XICs of one corn oil sample. **a** TIC chromatogram. **b** XIC of MRM 317.1/131.1 Da ZEN. **c** XIC of MRM 335.0/185.0 Da 13C-ZEN

Calibration Curve, LOD, and LOQ of the IDA–MRM–EPI Method

The limit of detection (LOD) was found to average 0.20 μg kg^{-1} for ZEN. Therefore, the method showed good performance at low statutory limits. The limit of quantification (LOQ) was acceptable. Within the defined calibration range, the calibration curve for ZEN showed satisfactory linearity, with correlation coefficient (R) greater than 0.995 (Table 2).

Accuracy and Precision of the IDA–MRM–EPI Method

The average recovery and relative standard deviation for reproducibility (RSD_R) of the analytical method applied to ZEN in samples are shown in Tables 3 and 4. Recovery ranged from 86.6 to 97.2%. The RSD_R values ranged from 4.1 to 6.2%. All were within the acceptable ranges, indicating the good accuracy and precision of this analytical method.

Analysis of Real Samples Using the IDA–MRM–EPI Method

The pollution level was high, and among the 51 samples, 42 samples (82.4%) were contaminated with ZEN. The concentration was between 1.71 and 179 μg kg^{-1}. All were within the commission regulations in China. Twelve samples (23.6%) were above 100 μg kg^{-1}. Eighteen samples (35.3%) were between 50 and 100 μg kg^{-1}, three samples (5.88%) were between 10 and 50 μg kg^{-1}, and 9 samples (17.6%) were below 10 μg kg^{-1}. The result showed the high contamination of ZEN in corn oil. Among the 42 incurred samples, 30 samples were above 50 μg kg^{-1}, indicating the content level was relatively

Table 2 Calibration curve, linear range, correlation coefficient (R), and limit of detection (LOD) and quantification (LOQ) of ZEN using the IDA–MRM–EPI method

Analyte	Calibration curve	Linear range (ng mL^{-1})	R ($1/X^2$)	Corn oil	
				LOD (μg kg^{-1})	LOQ (μg kg^{-1})
ZEN	$y = 0.87998x + 0.18270$	0.05–20.0	0.99550	0.20	0.60

Table 3 Intra-day accuracy and precision (n=3)

Compound	Spiked (μg kg^{-1})	Corn oil	
		Recovery (%)	RSD (%)
ZEN	0.6	87.3	6.2
	6	91.4	5.0
	60	95.6	4.9

Table 5 Occurrence of ZEN in foods in 2017–2019 in Jiaxing, China (μg kg^{-1})

Corn oil				
	Mean	Min	Max	Number of incurred samples
ZEN	57.0	1.71	179	42

Mean—the arithmetic mean value of the total sample

high, although they were within the commission regulations. Therefore, the corn oil was very easily polluted with ZEN (Tables 5 and 6).

Confirmation of Target Analytes

In the IDA experiment, MRM was used as the survey scan and EPI was used as the dependent scan for the same injection. As a result, criteria used to identify target compounds in the samples provided a MRM transition spectrum at the correct retention time, as obtained with both molecular and fragment ion data that can be used for in-house library search-based identification. The in-house library was constructed using the pure standard solutions.

Using the IDA experiment, the UPLC–MS/MS MRM chromatograms of these samples regarding the ZEN were triggered to obtain synchronous EPI spectra, which could be used to confirm the targets. Ten corn oil samples confirmed to contain ZEN using this method. As shown in Fig. 4, ZEN at 7.48 min showed obvious protonated molecular ions at m/z 317.0, 131.0, and 175.0.

The MS/MS spectra of ZEN in positive samples were searched against the library. The MS/MS spectrum of ZEN in corn oil matched well with the standard spectrum in the library (Fig. 5).

Discussion

Corn oil was extracted from corn germ. The characteristic of this oil is that the proportion of unsaturated fatty acid was up to 80~ 85% in the whole fatty acid. This oil does not contain cholesterol, which has a dissolving effect on the accumulation of cholesterol in the blood. So it can reduce the hardening effect on blood vessels, preventing and curing senile diseases such as arteriosclerosis and diabetes.

Sample preparation was performed using Xu's method for cereals and products. This extraction method was applied to corn oil. An efficient and convenient UPLC–ESI$^-$–MS/MS method using MRM–IDA–EPI mode was developed for the determination of ZEN in these samples. The samples were extracted directly using solvent, with no column purification required. The extract obtained also do not require drying under nitrogen. Using high-speed centrifugation allowed filtration to be omitted. Recoveries ranged from 86.6 to 97.2% and RSD_R values were within acceptable ranges, indicating the good accuracy and precision of this extraction method. Therefore, this method is suitable for the extraction of ZEN from corn oil. It showed considerable advantages, considering environmental impacts, efficiency, and reliability.

Table 4 Inter-day accuracy and precision (n=15)

Compound	Spiked (μg kg^{-1})	Corn oil	
		Recovery (%)	RSD (%)
ZEN	0.6	86.6	5.8
	6	91.5	4.9
	60	97.2	4.1

Table 6 The content of the ZEN in the 42 samples

Corn oil				
	>100 μg kg^{-1}	50–100 μg kg^{-1}	10–50 μg kg^{-1}	<10 μg kg^{-1}
ZEN	113.6	54.9	10.6	6.3
	133	57.8	25.6	1.71
	109	60.7	36.4	6.13
	179	57.7		4.36
	115.6	90.7		3.54
	128.9	88.2		5.62
	102.8	58.9		9.12
	164.7	66.9		6.68
	157.6	74.4		2.17
	104.5	51.3		
	121.6	53.6		
	132.6	59.8		
		74.9		
		81.6		
		66.7		
		95.6		
		74.5		
		57.9		

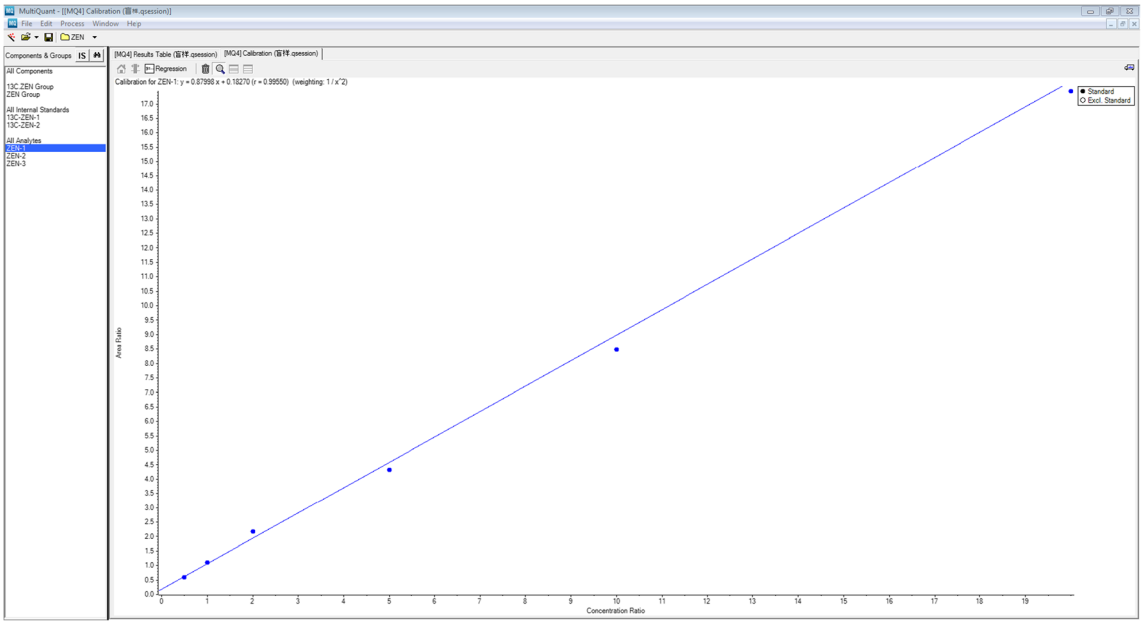

Fig. 4 Standard curve of the ZEN

In the recent years, liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) has become the most universal approach for mycotoxin analysis. The application of LC-MS/MS has allowed to quantify in overlapping peaks and reduce running times. Besides, narrower peaks can be obtained, which result in increased sensitivity. LC coupled to triple quadrupole mass spectrometer (QqQ) is at present considered as one of the most selective and sensitive techniques for quantification and confirmation of mycotoxins.

MRM-triggered EPI scans using IDA are effective for increasing the information obtained from a single injection. In MRM–IDA–EPI mode, simultaneously qualitative and quantitative analyses of the target analytes could be performed in one run to ensure accurate and reliable final data. Good performance

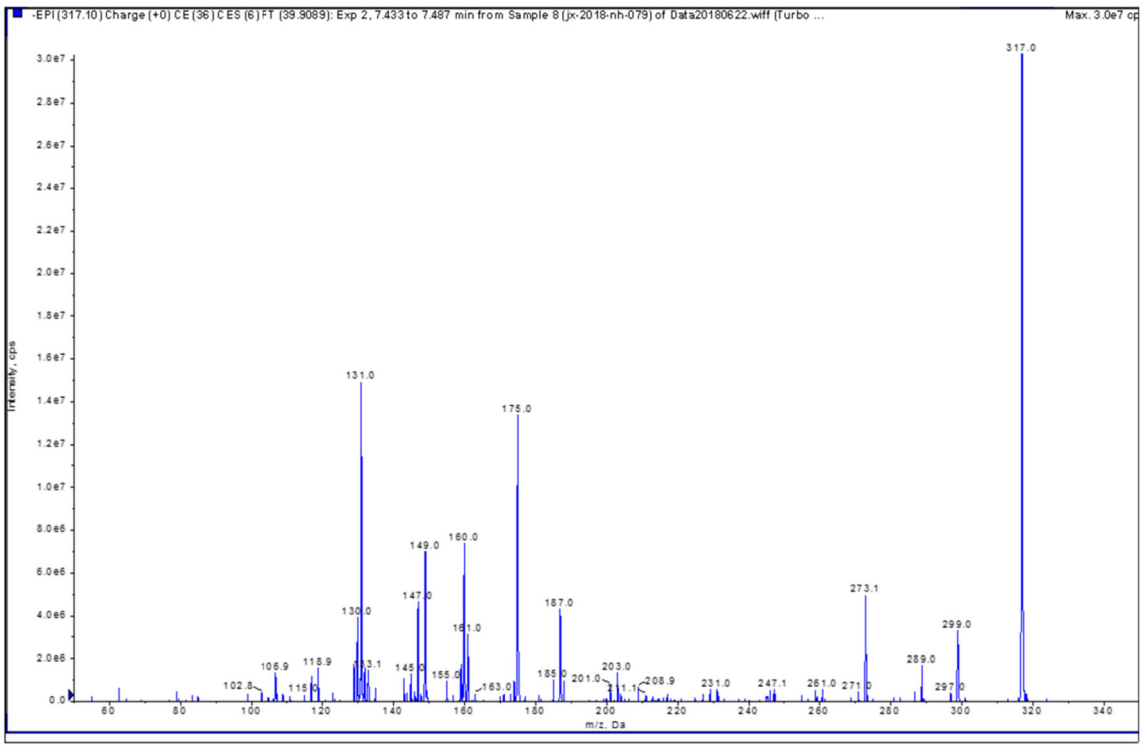

Fig. 5 EPI spectrum of ZEN in one corn oil sample. EPI, enhanced product ion

was obtained for the optimized method in terms of the LOQs, linearity, accuracy, and precision. False positives and negatives were successfully avoided using MS/MS library searching.

ZEN was detected in 42 samples within all 51 samples, and the detection rate was very high, demonstrating the widespread pollution in the corn oil, although they were not exceeding the regulation. As corn oil is widely used in China, perhaps more emphasis should be placed on their aflatoxin levels. The foodstuff, production technology, processing, and storage conditions should also be examined.

Most current sample preparations of ZEN used clean-up methods based on solid-phase extraction, which require column purification that is costly and complex. Compared with previous studies, a more reliable LC-MS/MS method for the simultaneous determination of ZEN in the corn oil was described. The sample pretreatment was simple in this method, and corn oil was extracted directly using solvent, with no column purification or derivatization required, while in the standard method, they need column purification and derivatization. The UPLC–ESI^-–MS/MS method we described has a much lower detection limit 0.20 μg kg^{-1} compared with standard method 10 μg kg^{-1}. The MRM combined EPI method should be stable enough to avoid false negative or false positive results. The analyte was completely separated in less than 9 min, affording narrow peaks with good peak symmetry. The quantitative and qualitative analysis can be performed simultaneously in MRM–IDA–EPI mode. The sample pretreatment and LC–MS methods developed in this research, from a convenience and analysis time perspective, are simple, efficient, cheaper, and less time consuming than existing methods.

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Declarations

Ethical Approval This article does not contain any studies with human participants performed by any of the authors.

Informed Consent None

Conflict of Interest Shencong Lv declares that he has no conflict of interest. Xiaoqiong Wu declares that she has no conflict of interest. Jian Guan declares that he has no conflict of interest. Yong Yan declares that he has no conflict of interest. Miaohua Ge declares that he has no conflict of interest. Guoying Zhu declares that she has no conflict of interest.

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