

## QuEChERS-超高效液相色谱串联质谱法定性筛查中药材熊胆粉中 169种兽药残留

孙 健, 胡 青, 诸艳蓉, 张 甦, 于 泓, 冯 睿, 张静娴, 毛秀红, 季 申\*

(上海市食品药品检验所, 国家药品监督管理局中药质量控制重点实验室, 上海 201203)

**摘要:** 建立了 QuEChERS-超高效液相色谱串联质谱法定性筛查中药材熊胆粉中多种兽药残留, 包括  $\beta$ -受体激动剂与拮抗剂、抗生素 (青霉素类、头孢菌素类、磺胺类、喹诺酮类、氯霉素类、四环素类、硝基咪唑类、大环内酯类、聚醚类等)、抗病毒药、驱虫药、甾体激素、非甾体抗炎药和镇静剂等 169 种兽药残留。样品经  $\text{Na}_2\text{EDTA}$ -McIlvaine 缓冲液和 5% 甲酸乙腈提取, 经分散固相萃取法净化, 以超高效液相色谱串联三重四极杆质谱法测定, 通过离子丰度比定性判定。169 种化合物检出限为  $1\sim 1\,000\ \mu\text{g}\cdot\text{kg}^{-1}$ 。本方法简便快速, 已应用于实际样品的测定, 并可扩展至其他类似药材基质的检测。

**关键词:** QuEChERS; 超高效液相色谱串联质谱; 兽药; 熊胆粉; 定性筛查

中图分类号: R917 文献标识码: A 文章编号: 0513-4870(2020)01-0113-10

## Qualitative screening of 169 veterinary drug residues in bear bile powder by QuEChERS-ultra high performance liquid chromatography-tandem mass spectrometry

SUN Jian, HU Qing, ZHU Yan-rong, ZHANG Su, YU Hong, FENG Rui,  
ZHANG Jing-xian, MAO Xiu-hong, JI Shen\*

(NMPA Key Laboratory for Quality Control of Traditional Chinese Medicine, Shanghai Institute for Food and Drug Control, Shanghai 201203, China)

**Abstract:** A QuEChERS-ultra high performance liquid chromatography-tandem mass spectrometry method was developed for qualitative screening of 169 veterinary drug residues in bear bile powder, including  $\beta$ -agonists and inhibitors, antibiotics (penicillins,  $\beta$ -lactams, sulfonamides, quinolones, chloramphenicals, tetracyclines, nitroimidazoles, macrolides, polyethers, etc.), antiviral drugs, anthelmintics, steroid hormones, nonsteroidal anti-inflammatory drugs (NSAIDs) and sedatives. The samples were extracted by  $\text{Na}_2\text{EDTA}$ -McIlvaine buffer solution and 5% formic acid-acetonitrile solution, then purified by dispersive solid phase extraction. Detection of veterinary drug residues by ultra high performance liquid chromatography-triple quadrupole mass spectrometry was conducted and qualitative confirmed by ion ratios. The limits of detection of 169 veterinary drugs were  $1\sim 1\,000\ \mu\text{g}\cdot\text{kg}^{-1}$ . The method is simple and fast, which had been used for the analysis of actual samples, and can be extended to the detection of similar matrix.

**Key words:** QuEChERS; ultra high performance liquid chromatography-tandem mass spectrometry; veterinary drug; bear bile powder; qualitative screening

收稿日期: 2019-07-05; 修回日期: 2019-08-21.

基金项目: 国家中药标准化项目 (ZYBZH-C-SH-48); 上海市科委技术平台项目 (18DZ2292200); 上海市科委技术标准专项 (18DZ2200900); 上海市科委课题 (18395810300).

\*通讯作者 Tel: 86-21-50798195, E-mail: jishen2013@163.com

DOI: 10.16438/j.0513-4870.2019-0531

兽药广泛用于动物养殖过程中,规范使用兽药可有效减少动物病患,但若违规超量超范围使用兽药,将对食品药品安全带来风险。目前,动物源性食品中兽药残留带来的安全风险已成为共识,政府及社会给予的重视程度较高。但动物源性中药材,在动物养殖过程中滥用兽药的情况同样存在,针对此类基质的检测方法研究及限量规定目前仍为空白,急需引起关注和加深研究,从源头进行有效控制。

熊胆粉为熊胆汁的干燥品。在黑熊胆囊手术引流胆汁过程中,需使用塞拉唑等镇静剂、青霉素等抗生素;术后恢复过程使用氧氟沙星等抗生素。另外,对某基地的黑熊饲养饲料进行检测,检出土霉素、四环素、喹乙醇等兽药。因此有必要对熊胆粉的多种兽药残留进行监控。

针对动物源性食品的兽药残留检测研究较多,相关国标(GB/T 22338-2008、GB/T 21317-2007、GB/T 21312-2007等)多按化合物类别分别检测;文献<sup>[1-8]</sup>方法大多研究多种兽药残留的快速测定方法。文献报道的食品中兽药残留检测的前处理方法有液液萃取法<sup>[1]</sup>、载体辅助液液萃取法<sup>[2]</sup>、固相萃取法<sup>[3,4]</sup>、QuEChERS法<sup>[5,6]</sup>等,检测技术有高效液相色谱法<sup>[7]</sup>、高效液相色谱串联三重四极杆质谱法<sup>[5,6]</sup>、高效液相色谱串联四极杆飞行时间质谱法<sup>[8]</sup>、高效液相色谱串联三重四极杆线性离子阱质谱法<sup>[9]</sup>、高效液相色谱串联四极杆静电场轨道阱质谱法<sup>[10]</sup>等。

动物类中药材基质复杂,多为干物质,药效成分多,不易净化,较食品检测更为困难。本文研究对象熊胆粉,牛磺熊去氧胆酸和牛磺鹅去氧胆酸等胆汁酸占44%~61%<sup>[11]</sup>,与多数弱酸性小分子药物化学结构有相似性,因去除困难而对检测带来较强干扰;其他成分还包括胆红素、蛋白质、氨基酸和微量元素等,是基质非常复杂的动物类中药材。因此需根据中药材的特殊性质,针对性地研究开发与食品不同的前处理方法和检测条件。

根据农业部235号公告<sup>[12]</sup>及相关国标,结合市场调研以及实际样品中的检测情况,本文采用QuEChERS法对熊胆粉样品进行前处理,以超高效液相色谱串联三重四极杆质谱法定性测定熊胆粉药材中的兽药残留共检测169种兽药,主要包括: $\beta$ -受体激动剂与拮抗剂、抗生素(青霉素类、头孢菌素类、磺胺类、喹诺酮类、氯霉素类、四环素类、硝基咪唑类、大环内酯类、聚醚类等)、抗病毒药、驱虫药(苯并咪唑类等)、甾体激素、非甾体抗炎药和镇静剂。

## 材料与方法

**仪器与试剂** Agilent 1290/6495超高效液相色谱串联三重四极杆质谱仪(美国Agilent公司),N-EVAPTM

112型氮吹仪(美国Organomation公司);IKA KS260C振荡器和IKA MS 2涡旋混合器(德国IKA公司)。

兽药对照品:青霉素G采购自中国食品药品检定研究院,其余167种购自A Chemtek公司,见表1;乙腈、甲醇、乙酸均为色谱纯(美国MERCK公司);醋酸,分析纯(中国医药集团上海化学试剂公司);甲酸、甲酸铵、氟化铵,色谱纯(美国Sigma-Aldrich公司);吸附剂:N-丙基乙二胺(PSA)、石墨化炭黑(GCB)、十八烷基键合硅胶(C18)、硫酸镁均购于天津博纳艾杰尔科技有限公司。实际样品由上海凯宝药业股份有限公司购自其熊胆粉药材供货商。

**色谱和质谱条件** Agilent Zorbax Eclipse plus C18 (3.0 mm×150 mm, 1.8  $\mu$ m)为色谱柱,以0.2%甲酸(含5 mmol·L<sup>-1</sup>甲酸铵和0.5 mmol·L<sup>-1</sup>氟化铵)溶液为流动相A,以0.2%甲酸乙腈溶液为流动相B,梯度洗脱程序:0~0.5 min, 2% B; 0.5~1.8 min, 2% B~15% B; 1.8~3.5 min, 15% B~20% B; 3.5~6 min, 20% B~25% B; 6~7 min, 25% B~30% B; 7~11 min, 30% B~35% B; 11~16 min, 35% B~100% B; 16~26 min, 100% B。柱温40 °C,流速0.5 mL·min<sup>-1</sup>,进样量1  $\mu$ L。

离子源:电喷雾离子(ESI)源;离子源温度:200 °C;毛细管电压:4 kV;干燥气流量:12 L·min<sup>-1</sup>;雾化气压力:25 psi (1 psi≈6.9 kPa);鞘气温度:250 °C;鞘气流量:10 L·min<sup>-1</sup>;喷嘴电压:500 V;采用多反应监测(MRM)方式检测。各化合物质谱参数见表2。

**标准溶液制备方法** 对照品储备溶液(100  $\mu$ g·mL<sup>-1</sup>):精密称取各对照品适量,根据溶解性,加适宜溶剂(表1)制成每1 mL含100  $\mu$ g的溶液,即得。

混合对照品溶液(1  $\mu$ g·mL<sup>-1</sup>):精密量取对照品储备溶液(100  $\mu$ g·mL<sup>-1</sup>)适量,用15%乙腈制成每mL含1  $\mu$ g的溶液,即得。

基质混合对照品溶液的制备:取空白熊胆粉样品(未检出上述169种兽药残留)适量,研细,混匀,取约0.1 g,精密称定,置于50 mL聚苯乙烯具塞离心管中,精密加入混合对照品溶液(1  $\mu$ g·mL<sup>-1</sup>)100  $\mu$ L,同供试品溶液的制备方法处理,即得。

**供试品溶液制备方法** 取熊胆粉样品适量,研细,混匀,取约0.1 g,精密称定,置于50 mL聚苯乙烯具塞离心管中,加0.1 mol·L<sup>-1</sup> Na<sub>2</sub>EDTA-McIlvaine缓冲液(称取2.9 g柠檬酸一水合物、10.9 g磷酸氢二钠十二水合物、37.2 g乙二胺四乙酸二钠二水合物,加水至900 mL,用1 mol·L<sup>-1</sup>氢氧化钠溶液调至pH 4.0,用水定容至1 L)10 mL,摇匀,涡旋使充分浸润。精密加入5%冰醋酸乙腈10 mL,涡旋使混匀,置振荡器上剧烈振荡(500次·min<sup>-1</sup>)10 min。加入无水氯化钠-硫酸钠(1:4)混合

粉末 5 g, 再置振荡器上剧烈振荡 (500 次 $\cdot$ min $^{-1}$ ) 3 min, 离心 5 min, 使分层。吸取上清液 6 mL, 置已预先装有净化材料的分散固相萃取净化管 [硫酸镁 300 mg, 十八烷基硅烷键合硅胶 300 mg, *N*-丙基乙二胺 (PSA) 1 800 mg] 中, 涡旋使充分混匀, 再置振荡器上剧烈振

荡 (500 次 $\cdot$ min $^{-1}$ ) 5 min 使净化完全, 离心 5 min, 精密吸取上清液 2 mL, 置氮吹仪上于 40 °C 水浴浓缩至干, 精密加 0.2 mL 15% 乙腈, 涡旋 1 min, 超声 1 min, 混匀, 离心, 取上清液, 即得。

定性判定方法 供试品溶液若检出与对照品保留

**Table 1** Information of the 169 reference compounds and LODs. a: Methanol; b: Acetonitrile; c: 25% Acetonitrile; d: 1% Formic acid-methanol; e: Methanol-dichloromethane (4:1); f: Methanol-water-acetonitrile (7:2:1); g: Acetonitrile-methanol (1:1); h: 1% Formic acid-acetonitrile

Category	Compound	CAS No.	Solvent	LOD/ $\mu$ g $\cdot$ kg $^{-1}$	
$\beta$ -Agonists	Cimaterol	54239-37-1	a	10	
	Clorprenaline	3811-25-4	a	10	
	Terbutaline	23031-32-5	a	1	
	Tulobuterol	56776-01-3	a	1	
	Clenbuterol	21898-19-1	a	10	
	Penbutolol	28163-36-2	a	10	
	Ractopamine	90274-24-1	a	1	
	Salbutamol	18559-94-9	a	1	
	$\beta$ -Inhibitors	Propranolol	318-98-9	a	100
Carazolol		57775-29-8	b	1	
Penicillins	Ampicillin	69-53-4	c	50	
	Oxacillin	66-79-5	c	250	
	Piperacillin	61477-96-1	c	10	
	Sulbactam	68373-14-8	c	50	
	Cloxacillin	7081-44-9	c	50	
	Dicloxacillin	13412-64-1	c	50	
	Penicilline V	132-98-9	c	50	
	Penicilline G	61-33-6	a	50	
$\beta$ -Lactams	Cefapirin	21593-23-7	c	10	
	Cefazolin	25953-19-9	c	10	
	Cefetamet pivoxyl	65243-33-6	c	10	
	Cefotaxime	63527-52-6	c	10	
	Ceftiofur	80370-57-6	c	10	
	Cephalonium	5575-21-3	c	10	
	Cefamandole	58648-57-0	c	50	
	Cefoperazone	62893-20-3	c	10	
	Cefquinome	118443-89-3	c	10	
	Sulfomamides	Sulfabenzamide	127-71-9	a	1
		Sulfacetamide	144-80-9	a	1
		Sulfachloropyridazine	80-32-0	a	1
		Sulfaclozine	102-65-8	a	50
Sulfadimethoxine		122-11-2	a	1	
Sulfaguandine		57-67-0	a	1	
Sulfamerazine		127-79-7	a	1	
Sulfamethizole		144-82-1	a	1	
Sulfamethoxazole		723-46-6	a	5	
Sulfamonomethoxine		1220-83-3	a	1	
Sulfamoxole		729-99-7	a	1	
Sulfaphenazole		526-08-9	a	50	
Sulfapyridine		144-83-2	a	1	
Sulfaquinoxaline		59-40-5	a	1	
Sulfathiazole		72-14-0	a	10	
Sulphisoxazole		127-69-5	a	10	
Sulfadiazine		68-35-9	a	1	
Sulfamethazine	57-68-1	a	1		
Sulfadoxine	2447-57-6	a	1		
Sulfameter	651-06-9	a	1		
Sulfamethoxy-pyridazine	80-35-3	a	10		
Sulfisomidine	515-64-0	a	10		

Continued

Category	Compound	CAS No.	Solvent	LOD/ $\mu\text{g}\cdot\text{kg}^{-1}$
Quinolones	Trimethoprim	738-70-5	a	10
	Ciprofloxacin	85721-33-1	d	100
	Danofloxacin	112398-08-0	d	50
	Difloxacin	98106-17-3	d	50
	Enoxacin	74011-58-8	d	250
	Enrofloxacin	93106-60-6	d	10
	Fleroxacin	79660-72-3	d	10
	Lomefloxacin	98079-51-7	d	50
	Nalidixic acid	389-08-2	d	10
	Norfloxacin	70458-96-7	d	500
	Ofloxacin	82419-36-1	d	100
	Orbifloxacin	113617-63-3	d	1
	Oxolinic acid	14698-29-4	d	10
	Pefloxacin	70458-92-3	d	100
	Sarafloxacin	98105-99-8	d	50
	Sparfloxacin	110871-86-8	d	50
	Flumequine	42835-25-6	d	10
	Chloramphenicals	Marbofloxacin	115550-35-1	a
Nequinatate		13997-19-8	e	1
Chloramphenicol		56-75-7	a	10
Tetracyclines	Florfenicol	73231-34-2	a	10
	Thiamphenicol	15318-45-3	a	10
	Oxytetracycline	2058-46-0	a	100
	Tetracycline	60-54-8	a	500
Nitroimidazoles	Chlortetracycline	64-72-2	a	100
	Doxycycline	24390-14-5	a	1 000
	Metronidazole	443-48-1	a	100
	Hydroxydimetridazole	936-05-0	a	100
	Hydroxymetronidazole	4812-40-2	a	10
Macrolides	Dimetridazole	551-92-8	a	100
	Ronidazole	7681-76-7	a	10
	Erythromycin	114-07-8	a	10
	Oleandomycin	7060-74-4	a	10
	Tylosin	1401-69-0	a	1
	Tylvalosin	63428-13-7	a	10
	Avermectin B1a	71751-41-2	a	50
	Doramectin	117704-25-3	a	10
	Eprinomectin B1a	123997-26-2	a	50
	Ivermectin B1a	70288-86-7	a	10
Polyethers	Kitasamycin	1392-21-8	a	10
	Maduramicin	84878-61-5	a	1
	Monensin	22373-78-0	a	1
Other antibiotics	Nigericin	28643-80-3	a	10
	Dapson	80-08-0	a	1
	<i>N</i> -Acetyl dapson	565-20-8	a	1
	Lincomycin	859-18-7	a	10
	Valnemulin	133868-46-9	a	10
	Olaquinox	23696-28-8	f	500
Antiviral drugs	3-Methyl-quinoxaline-2-carboxylic acid	74003-63-7	f	500
	Amantadine	768-94-5	a	250
Anthelmintics	2-Aminoflubendazole	82050-13-3	g	1
	5-Hydroxymebendazole	60254-95-7	g	1
	Albendazole	54965-21-8	g	1
	Albendazole sulfone	75184-71-3	g	10
	Albendazole sulfoxide	54029-12-8	g	1
	Cambendazole	26097-80-3	g	1
	Fenbendazole	43210-67-9	g	1
	Flubendazole	31430-15-6	g	1
	Mebendazole	31431-39-7	g	1
	Oxfendazole	53716-50-0	g	1

Continued				
Category	Compound	CAS No.	Solvent	LOD/ $\mu\text{g}\cdot\text{kg}^{-1}$
	Oxfendazole sulfone	54029-20-8	g	1
	Oxibendazole	20559-55-1	g	1
	Thiabendazole	148-79-8	g	10
	Triclabendazole	68786-66-3	g	10
	Hydroxy-thiabendazole	948-71-0	g	10
	Mebendazole-amine	52329-60-9	g	10
	Clopidol	2971-90-6	a	10
	Diclazuril	101831-37-2	a	1
	Ethopabate	1959/6/3	a	1
	Febantel	58306-30-2	a	1
	Nitroxynil	1689-89-0	a	10
	Zoalene	148-01-6	a	10
	Halofuginone	64924-67-0	a	50
	Levamisole	16595-80-5	a	50
	Nicarbazine	330-95-0	a	1
	Basic violet 3	548-62-9	h	1
	Robenidine	25875-50-7	a	10
	Leucomalachite green	129-73-7	a	1
Steroid hormones	Betamethasone	378-44-9	b	10
	Dexamethasone	1950/2/2	b	10
	Flumethasone	2135-17-3	b	50
	Hydrocortisone	50-23-7	b	100
	Methylprednisolone	83-43-2	b	10
	Prednisolone	50-24-8	b	100
	Prednisone	1953/3/2	b	100
	Triamcinolone	124-94-7	b	1
	Triamcinolone acetonide	76-25-5	b	10
	Fludrocortisone acetate	514-36-3	b	250
	Cortisone acetate	1950/4/4	b	500
	Testosterone	58-22-0	b	50
	Testosterone propionate	57-85-2	b	50
	Methyltestosterone	58-18-4	b	50
	Nandrolone phenlpropionate	62-90-8	b	100
	Trenbolone	10161-33-8	b	100
	Progesterone	57-83-0	b	50
	Megestrol acetate	595-33-5	b	10
	Melengestrol acetate	2919-66-6	b	50
	Chlormadinone acetate	302-22-7	b	10
NSAIDs	4-Acetamido antipyrine	83-15-8	b	1
	4-Formylamino antipyrine	1672-58-8	b	1
	Carprofen	53716-49-7	b	100
	Diclofenac	15307-86-5	b	10
	Indomethacin	53-86-1	b	50
	Indoprofen	31842-01-0	b	10
	Mefenamic acid	61-68-7	b	1
	Meloxicam	71125-38-7	b	10
	Piroxicam	36322-90-4	b	50
	Sulindac	38194-50-2	b	10
	Tenoxicam	59804-37-4	b	10
	Tolfenamic acid	13710-19-5	b	250
	Tolmetin	26171-23-3	b	10
Sedatives	Acepromazine	3598-37-6	b	1
	Azaperol	2804/5/9	b	10
	Azaperone	1649-18-9	b	1
	Chlorpromazine	69-09-0	b	10
	Diazepam	439-14-5	a	10
	Haloperidol	52-86-8	b	1
	Methaqualone	72-44-6	a	100
	Propionylpromazine	7681-67-6	b	10
	Xylazine	7361-61-7	a	1

**Table 2** MS parameters of the 169 veterinary drugs

No.	Compound	Precursor ion ( <i>m/z</i> )	Product ion ( <i>m/z</i> )	CE/V	Ionization mode	RT/min
1	2-Aminoflubendazole	256.1	123.0, 95.0	40, 40	[M+H] <sup>+</sup>	8.04
2	3-Methyl-quinoxaline-2-carboxylic acid	189.1	145.0, 143.0	12, 16	[M+H] <sup>+</sup>	5.38
3	4-Acetamido antipyrine	246.1	227.9, 83.0	12, 40	[M+H] <sup>+</sup>	4.76
4	4-Formylamino antipyrine	232.1	104.0, 83.0	20, 20	[M+H] <sup>+</sup>	4.79
5	5-Hydroxymebendazole	298.1	266.1, 79.1	25, 44	[M+H] <sup>+</sup>	7.64
6	Acepromazine	327.2	86.1, 58.1	20, 48	[M+H] <sup>+</sup>	11.74
7	Albendazole	266.1	234.1, 191.0	16, 32	[M+H] <sup>+</sup>	12.75
8	Albendazole sulfone	298.1	266.1, 159.0	20, 40	[M+H] <sup>+</sup>	8.50
9	Albendazole sulfoxide	282.1	239.9, 208.0	12, 24	[M+H] <sup>+</sup>	6.31
10	Amantadine	152.1	135.0, 77.1	18, 50	[M+H] <sup>+</sup>	5.18
11	Ampicillin	350.0	114.0, 106.0	36, 16	[M+H] <sup>+</sup>	4.42
12	Avermectin B1a	895.5	751.4, 449.3	48, 48	[M+Na] <sup>+</sup>	18.02
13	Azaperol	330.2	312.1, 121.0	16, 20	[M+H] <sup>+</sup>	5.94
14	Azaperone	328.2	165.1, 121.1	20, 20	[M+H] <sup>+</sup>	7.03
15	Basic violet 3	372.3	356.1, 340.0	44, 55	[M+H] <sup>+</sup>	15.01
16	Betamethasone	393.2	373.2, 355.2	4, 8	[M+H] <sup>+</sup>	13.01
17	Cambendazole	303.1	261.0, 217.1	16, 32	[M+H] <sup>+</sup>	8.34
18	Carazolol	299.2	222.0, 116.0	20, 20	[M+H] <sup>+</sup>	8.54
19	Carprofen	272.0	227.9, 225.9	12, 28	[M-H] <sup>-</sup>	15.16
20	Cefamandole	463.1	347.0, 158.0	4, 16	[M+H] <sup>+</sup>	8.05
21	Cefapirin	424.1	291.9, 151.9	12, 28	[M+H] <sup>+</sup>	3.74
22	Cefazolin	455.0	323.0, 156.0	8, 11	[M+H] <sup>+</sup>	5.58
23	Cefetamet pivoxyl	512.1	241.0, 57.1	16, 48	[M+H] <sup>+</sup>	14.23
24	Cefoperazone	646.2	530.2, 143.0	8, 45	[M+H] <sup>+</sup>	7.21
25	Cefotaxime	456.1	324.0, 125.0	8, 60	[M+H] <sup>+</sup>	5.11
26	Cefquinome	529.1	134.2, 125.0	8, 60	[M+H] <sup>+</sup>	4.39
27	Ceftiofur	524.0	241.0, 126.0	16, 40	[M+H] <sup>+</sup>	9.22
28	Cephalonium	459.1	337.0, 152.0	8, 20	[M+H] <sup>+</sup>	4.82
29	Chloramphenicol	321.0	152.1, 121.0	14, 36	[M-H] <sup>-</sup>	9.19
30	Chlorpromazine	319.1	86.1, 58.2	16, 44	[M+H] <sup>+</sup>	13.66
31	Chlortetracycline	479.1	444.0, 154.1	20, 36	[M+H] <sup>+</sup>	7.95
32	Chlormadinone acetate	405.2	345.0, 309.0	12, 16	[M+H] <sup>+</sup>	16.12
33	Cimaterol	220.1	202.1, 143.1	4, 20	[M+H] <sup>+</sup>	3.57
34	Ciprofloxacin	332.1	314.0, 231.0	20, 48	[M+H] <sup>+</sup>	5.23
35	Clenbuterol	277.1	259.1, 203.0	4, 12	[M+H] <sup>+</sup>	6.75
36	Clopidol	192.1	101.0, 51.0	25, 48	[M+H] <sup>+</sup>	4.23
37	Clorprenaline	214.1	196.0, 153.9	8, 12	[M+H] <sup>+</sup>	5.62
38	Cloxacillin	436.0	277.0, 160.0	12, 12	[M+H] <sup>+</sup>	14.00
39	Cortisone acetate	403.2	343.1, 163.0	20, 28	[M+H] <sup>+</sup>	14.28
40	Danofloxacin	358.2	340.1, 82.1	20, 48	[M+H] <sup>+</sup>	5.56
41	Dapson	249.1	156.0, 92.0	10, 28	[M+H] <sup>+</sup>	7.25
42	Dexamethasone	393.2	373.2, 355.2	2, 6	[M+H] <sup>+</sup>	12.88
43	Diazepam	285.1	193.1, 153.9	37, 29	[M+H] <sup>+</sup>	14.91
44	Diclazuril	405.0	334.8, 334.0	16, 20	[M-H] <sup>-</sup>	15.58
45	Diclofenac	296.0	215.1, 214.1	16, 48	[M+H] <sup>+</sup>	15.45
46	Dicloxacillin	470.0	310.8, 159.9	12, 12	[M+H] <sup>+</sup>	14.53
47	Difloxacin	400.1	356.2, 299.1	16, 32	[M+H] <sup>+</sup>	6.92
48	Dimetridazole	142.1	96.1, 81.1	16, 28	[M+H] <sup>+</sup>	4.72
49	Doramectin	921.5	777.4, 449.3	44, 56	[M+Na] <sup>+</sup>	18.55
50	Doxycycline	445.2	428.1, 321.1	16, 28	[M+H] <sup>+</sup>	8.30
51	Enoxacin	321.1	303.3, 231.8	16, 40	[M+H] <sup>+</sup>	4.83
52	Enrofloxacin	360.2	316.2, 245.1	16, 32	[M+H] <sup>+</sup>	5.84
53	Eprinomectin B1a	936.5	490.2, 352.1	56, 60	[M+Na] <sup>+</sup>	17.42
54	Erythromycin	734.5	576.3, 158.1	16, 32	[M+H] <sup>+</sup>	11.35
55	Ethopabate	238.1	205.9, 135.9	4, 36	[M+H] <sup>+</sup>	9.80
56	Febantel	447.1	415.1, 383.1	10, 16	[M+H] <sup>+</sup>	15.66
57	Fenbendazole	300.1	268.1, 159.0	20, 36	[M+H] <sup>+</sup>	14.31
58	Fleroxacin	370.1	326.0, 268.9	20, 24	[M+H] <sup>+</sup>	5.11
59	Florfenicol	356.0	185.1, 119.0	12, 28	[M-H] <sup>-</sup>	8.43
60	Flubendazole	314.1	282.1, 123.0	20, 36	[M+H] <sup>+</sup>	13.08

Continued

No.	Compound	Precursor ion ( <i>m/z</i> )	Product ion ( <i>m/z</i> )	CE/V	Ionization mode	RT/min
61	Fludrocortisone acetate	423.2	239.0, 121.0	24, 40	[M+H] <sup>+</sup>	14.05
62	Flumequine	262.1	244.1, 202.0	12, 32	[M+H] <sup>+</sup>	12.90
63	Flumethasone	411.2	391.1, 253.1	4, 12	[M+H] <sup>+</sup>	13.04
64	Halofuginone	416.0	138.0, 395.8	16, 12	[M+H] <sup>+</sup>	8.53
65	Haloperidol	376.1	165.0, 122.9	24, 48	[M+H] <sup>+</sup>	11.83
66	Hydroxydimetridazole	158.1	140.0, 55.2	8, 20	[M+H] <sup>+</sup>	3.95
67	Hydrocortisone	363.4	121.1, 309.2	20, 20	[M+H] <sup>+</sup>	10.69
68	Hydroxymetronidazole	188.1	126.1, 123.1	16, 8	[M+H] <sup>+</sup>	3.52
69	Hydroxy-thiabendazole	218.0	191.0, 147.1	32, 40	[M+H] <sup>+</sup>	3.93
70	Indomethacin	358.1	138.9, 110.9	24, 68	[M+H] <sup>+</sup>	15.47
71	Indoprofen	282.1	236.1, 77.1	20, 76	[M+H] <sup>+</sup>	13.57
72	Ivermectin B1a	897.5	753.4, 183.0	52, 56	[M+Na] <sup>+</sup>	19.52
73	Kitasamycin	772.5	174.0, 108.9	36, 48	[M+H] <sup>+</sup>	13.43
74	Leucomalachite green	331.2	316.2, 239.2	20, 28	[M+H] <sup>+</sup>	16.95
75	Levamisole	205.1	178.1, 91.1	20, 44	[M+H] <sup>+</sup>	4.48
76	Lincomycin	407.2	126.1, 42.2	29, 75	[M+H] <sup>+</sup>	4.25
77	Lomefloxacin	352.2	308.2, 265.0	16, 25	[M+H] <sup>+</sup>	5.56
78	Maduramicin	939.5	895.6, 877.5	56, 36	[M+Na] <sup>+</sup>	21.81
79	Marbofloxacin	363.2	320.1, 72.2	12, 28	[M+H] <sup>+</sup>	4.82
80	Mebendazole	296.1	264.1, 77.0	20, 48	[M+H] <sup>+</sup>	12.03
81	Mebendazole-amine	238.1	105.1, 77.1	28, 40	[M+H] <sup>+</sup>	7.35
82	Mefenamic acid	242.1	224.1, 209.1	8, 28	[M+H] <sup>+</sup>	16.03
83	Megestrol acetate	385.2	325.2, 267.2	8, 12	[M+H] <sup>+</sup>	16.05
84	Melengestrol acetate	397.2	337.1, 279.0	12, 20	[M+H] <sup>+</sup>	16.19
85	Meloxicam	352.0	140.9, 115.0	16, 16	[M+H] <sup>+</sup>	14.58
86	Methaqualone	251.1	132.1, 91.0	37, 49	[M+H] <sup>+</sup>	13.84
87	Methylprednisolone	375.2	357.2, 161.1	4, 16	[M+H] <sup>+</sup>	12.53
88	Methyltestosterone	303.2	109.1, 97.1	32, 32	[M+H] <sup>+</sup>	14.91
89	Metronidazole	172.1	128.0, 82.1	12, 24	[M+H] <sup>+</sup>	3.99
90	Monensin	693.5	675.3, 461.3	40, 60	[M+H] <sup>+</sup>	20.87
91	<i>N</i> -Acetyl dapson	291.1	197.9, 155.8	12, 16	[M+H] <sup>+</sup>	8.12
92	Nalidixic acid	233.1	215.1, 159.1	20, 40	[M+H] <sup>+</sup>	12.12
93	Nandrolone phenylpropionate	407.3	257.2, 105.1	18, 36	[M+H] <sup>+</sup>	17.61
94	Nequinat	366.2	334.1, 91.0	16, 44	[M+H] <sup>+</sup>	15.23
95	Nicarbazine	301.1	137.0, 106.9	20, 45	[M-H] <sup>-</sup>	15.12
96	Nigericin	742.5	125.0, 107.0	60, 70	[M+NH <sub>4</sub> ] <sup>+</sup>	20.32
97	Nitroxynil	288.9	162.0, 127.0	20, 28	[M-H] <sup>-</sup>	12.80
98	Norfloxacin	320.1	302.1, 231.1	25, 40	[M+H] <sup>+</sup>	5.03
99	Ofloxacin	362.2	318.2, 261.1	20, 40	[M+H] <sup>+</sup>	5.08
100	Olaquinox	264.1	143.0, 102.0	40, 56	[M+H] <sup>+</sup>	3.58
101	Oleandomycin	688.3	544.3, 158.2	15, 25	[M+H] <sup>+</sup>	10.36
102	Orbifloxacin	396.2	352.1, 295.1	16, 28	[M+H] <sup>+</sup>	6.11
103	Oxacillin	402.0	243.0, 160.0	8, 8	[M+H] <sup>+</sup>	13.50
104	Oxfendazole	316.1	284.0, 159.0	16, 32	[M+H] <sup>+</sup>	8.62
105	Oxfendazole sulfone	332.1	300.1, 159.0	20, 40	[M+H] <sup>+</sup>	11.18
106	Oxibendazole	250.1	218.1, 176.1	16, 28	[M+H] <sup>+</sup>	8.94
107	Oxolinic acid	262.1	243.9, 159.9	20, 45	[M+H] <sup>+</sup>	9.17
108	Oxytetracycline	461.2	426.1, 201.1	14, 48	[M+H] <sup>+</sup>	5.18
109	Pefloxacin	334.2	290.1, 233.1	16, 28	[M+H] <sup>+</sup>	5.17
110	Penbutolol	292.2	236.0, 133.0	12, 24	[M+H] <sup>+</sup>	13.58
111	Penicilline G	335.1	176.0, 160.1	8, 8	[M+H] <sup>+</sup>	11.09
112	Penicilline V	351.1	159.9, 113.9	8, 40	[M+H] <sup>+</sup>	12.77
113	Piperacillin	518.2	143.0, 114.9	20, 70	[M+H] <sup>+</sup>	10.34
114	Piroxicam	332.1	95.0, 78.0	20, 76	[M+H] <sup>+</sup>	13.31
115	Prednisolone	361.2	343.2, 147.1	4, 24	[M+H] <sup>+</sup>	10.45
116	Prednisone	359.2	341.2, 147.1	10, 40	[M+H] <sup>+</sup>	10.50
117	Progesterone	315.2	109.0, 97.0	28, 24	[M+H] <sup>+</sup>	16.17
118	Propranolol	260.0	116.0, 56.0	16, 28	[M+H] <sup>+</sup>	9.56
119	Propionylpromazine	341.2	86.1, 58.1	20, 56	[M+H] <sup>+</sup>	13.51
120	Ractopamine	302.2	284.2, 164.1	8, 12	[M+H] <sup>+</sup>	5.51

Continued

No.	Compound	Precursor ion ( <i>m/z</i> )	Product ion ( <i>m/z</i> )	CE/V	Ionization mode	RT/min
121	Robenidine	334.1	155.0, 111.0	16, 56	[M+H] <sup>+</sup>	14.14
122	Ronidazole	201.1	140.1, 55.2	8, 25	[M+H] <sup>+</sup>	4.39
123	Salbutamol	240.2	166.1, 77.2	4, 60	[M+H] <sup>+</sup>	3.44
124	Sarafloxacin	386.1	368.1, 342.1	20, 20	[M+H] <sup>+</sup>	6.73
125	Sparfloxacin	393.2	349.0, 292.1	20, 28	[M+H] <sup>+</sup>	6.92
126	Sulbactam	232.0	140.1, 64.1	12, 44	[M-H] <sup>-</sup>	3.74
127	Sulfabenzamide	277.1	155.9, 92.0	12, 36	[M+H] <sup>+</sup>	9.72
128	Sulfacetamide	215.0	156.0, 92.0	8, 20	[M+H] <sup>+</sup>	4.17
129	Sulfachloropyridazine	285.0	156.0, 108.1	12, 24	[M+H] <sup>+</sup>	7.60
130	Sulfaclozine	285.0	155.9, 108.1	20, 24	[M+H] <sup>+</sup>	9.85
131	Sulfadiazine	251.1	108.1, 92.1	20, 28	[M+H] <sup>+</sup>	4.53
132	Sulfadimethoxine	311.1	156.0, 92.1	16, 36	[M+H] <sup>+</sup>	10.13
133	Sulfamethazine	279.1	186.1, 92.1	12, 38	[M+H] <sup>+</sup>	6.16
134	Sulfadoxine	311.1	156.0, 92.1	16, 32	[M+H] <sup>+</sup>	8.20
135	Sulfaguanidine	215.1	156.0, 108.0	12, 24	[M+H] <sup>+</sup>	2.68
136	Sulfamerazine	265.1	156.0, 92.1	12, 28	[M+H] <sup>+</sup>	5.37
137	Sulfameter	281.1	156.0, 92.0	20, 40	[M+H] <sup>+</sup>	6.25
138	Sulfamethizole	271.0	156.0, 92.0	9, 29	[M+H] <sup>+</sup>	6.07
139	Sulfamethoxazole	254.1	156.0, 92.1	12, 24	[M+H] <sup>+</sup>	8.25
140	Sulfamethoxypyridazine	281.1	108.1, 92.1	28, 32	[M+H] <sup>+</sup>	4.03
141	Sulfamonomethoxine	281.0	156.0, 126.0	10, 20	[M+H] <sup>+</sup>	7.10
142	Sulfamoxole	268.1	155.9, 108.0	20, 20	[M+H] <sup>+</sup>	5.67
143	Sulfaphenazole	315.1	158.1, 92.0	40, 40	[M+H] <sup>+</sup>	10.48
144	Sulfapyridine	250.1	156.0, 92.0	17, 29	[M+H] <sup>+</sup>	5.03
145	Sulfaquinoxaline	301.1	156.0, 92.0	16, 32	[M+H] <sup>+</sup>	10.19
146	Sulfathiazole	256.0	156.0, 92.1	12, 28	[M+H] <sup>+</sup>	4.74
147	Sulfisomidine	279.1	124.1, 92.0	20, 40	[M+H] <sup>+</sup>	4.03
148	Sulindac	357.1	248.1, 233.1	40, 40	[M+H] <sup>+</sup>	13.67
149	Sulphisoxazole	268.1	156.0, 92.0	10, 40	[M+H] <sup>+</sup>	8.81
150	Tenoxicam	338.0	121.0, 78.0	24, 72	[M+H] <sup>+</sup>	8.73
151	Terbutaline	226.1	152.1, 107.1	12, 28	[M+H] <sup>+</sup>	3.42
152	Testosterone	289.2	109.0, 97.0	32, 36	[M+H] <sup>+</sup>	14.51
153	Testosterone propionate	345.2	109.0, 97.1	36, 20	[M+H] <sup>+</sup>	17.24
154	Tetracycline	445.2	410.1, 154.2	17, 30	[M+H] <sup>+</sup>	5.79
155	Thiabendazole	202.0	175.0, 131.0	24, 36	[M+H] <sup>+</sup>	4.74
156	Thiamphenicol	354.0	289.9, 185.0	8, 16	[M-H] <sup>-</sup>	5.68
157	Tolfenamic acid	262.1	244.0, 209.1	12, 28	[M+H] <sup>+</sup>	16.20
158	Tolmetin	258.1	119.0, 91.0	24, 44	[M+H] <sup>+</sup>	14.09
159	Trenbolone	271.2	253.2, 199.1	20, 28	[M+H] <sup>+</sup>	13.57
160	Triamcinolone	395.2	375.0, 357.2	8, 12	[M+H] <sup>+</sup>	8.47
161	Triamcinolone acetonide	435.2	415.2, 397.1	8, 16	[M+H] <sup>+</sup>	13.57
162	Triclabendazole	361.0	345.9, 274.0	28, 40	[M+H] <sup>+</sup>	16.05
163	Trimethoprim	291.2	261.1, 123.1	24, 24	[M+H] <sup>+</sup>	4.92
164	Tulobuterol	228.1	154.0, 119.1	12, 32	[M+H] <sup>+</sup>	6.66
165	Tylosin	916.5	174.1, 101.0	40, 56	[M+H] <sup>+</sup>	12.47
166	Tylvalosin	1042.6	173.9, 109.1	45, 52	[M+H] <sup>+</sup>	14.39
167	Valnemulin	567.4	264.2, 263.0	16, 16	[M+H] <sup>+</sup>	13.65
168	Xylazine	221.1	90.0, 72.0	40, 40	[M+H] <sup>+</sup>	6.60
169	Zoalene	224.0	181.1, 77.0	12, 24	[M-H] <sup>-</sup>	8.11

时间相同的色谱峰,且所选择的离子丰度比与对照品溶液的离子丰度比一致(相对比例>50%,允许±20%偏差;相对比例20%~50%,允许±25%偏差;相对比例10%~20%,允许±30%偏差;相对比例<10%,允许±50%偏差),可判定具有该成分。

#### 方法学验证

**专属性** 取空白样品适量,同供试品溶液的制备

方法处理,进样测定。

**检出限** 取熊胆粉空白样品适量,研细,混匀,取约0.1 g,一式7份,精密称定,置于50 mL聚苯乙烯具塞离心管中,分别精密加入混合对照品溶液(100 ng·mL<sup>-1</sup>)1、10、50、100、250、500和1 000 μL,同供试品溶液的制备方法处理,进样测定。采用目视评价法,以真实最低检出浓度作为检出限。

重复性 在加样 ( $1\ 000\ \mu\text{g}\cdot\text{kg}^{-1}$ ) 水平进行重复性实验,一式6份,进样测定。

## 结果

### 1 方法学验证

**1.1 专属性** 空白样品未检出上述兽药残留,表明空白基质对测定无干扰。

**1.2 检出限** 上述169种化合物检出限为  $1\sim 1\ 000\ \mu\text{g}\cdot\text{kg}^{-1}$ , 详见表1。熊胆粉由熊胆汁干燥而得,产率约10%。按农业部235号公告暂定熊胆汁中兽药残留限量,并以产率折算至熊胆汁中,本方法检出限能够满足定性筛查的需要。

**1.3 重复性** 在加样 ( $1\ 000\ \mu\text{g}\cdot\text{kg}^{-1}$ ) 水平进行重复性

实验,一式6份,均检出上述兽药。各化合物MRM色谱图见图1。

### 2 实际样品测定

检测44批熊胆粉样品,其中17批检出,检出率38.6%,共检出19种兽药残留,具体情况见表3。

其中,由药材基地提供规范养殖的40批样品,13批检出,检出兽药种类少,主要包括氧氟沙星、3-甲基喹噁啉-2-羧酸(喹乙醇代谢物)、阿苯达唑亚砷(阿苯达唑代谢物)、4-乙酰胺基安替比林(安替比林代谢物),含量均较低。推测氧氟沙星为黑熊术后恢复用药,喹乙醇为饲料带入。而购自市场的4批劣质药材,均检出多种兽药残留,且含量很高。可见中药材规范养殖或种植的必要性。

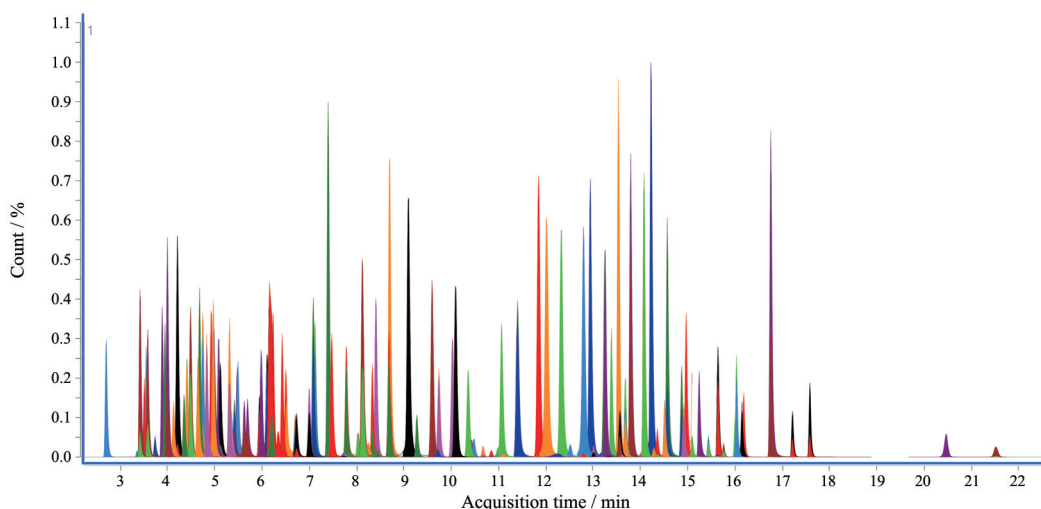


Figure 1 MRM chromatograms of the 169 veterinary drugs

Table 3 The detection results of positive results

Supplier	Result
Medicinal material base	Ofloxacin, 3-methyl-quinoxaline-2-carboxylic acid
	Albendazole sulfoxide
	Ofloxacin
	Ofloxacin
	Ofloxacin
	4-Acetamido antipyrine, ofloxacin
	Ofloxacin
	Ofloxacin
	4-Acetamido antipyrine, 4-formylamino antipyrine, ofloxacin, diclofenac
	Metronidazole, 4-acetamido antipyrine, 4-formylamino antipyrine, ofloxacin, enrofloxacin
	Ofloxacin
	Ivermectin
	4-Acetamido antipyrine, 4-formylamino antipyrine, ivermectin
Open market	Hydroxymetronidazole, metronidazole, lincomycin, albendazole sulfoxide, albendazole sulfone
	Olaquinox, 4-acetamido antipyrine, 4-formylamino antipyrine, 3-methyl-quinoxaline-2-carboxylic acid, albendazole sulfoxide, albendazole
	Sulfamethoxypyridazine, 4-acetamido antipyrine, 4-formylamino antipyrine, trimethoprim, 3-methyl-quinoxaline-2-carboxylic acid, sulfameter, sulfamonomethoxine, diclofenac, monensin
	Hydroxymetronidazole, metronidazole, 4-acetamido antipyrine, 4-formylamino antipyrine, 3-methyl-quinoxaline-2-carboxylic acid

## 讨论

目前,多兽药残留同时测定的前处理方法主要包括EMR-Lipid固相萃取法和QuEChERS法。但EMR-Lipid固相萃取法对长链结构物质具较强吸附力,能有效降低肉类等高脂肪食品的基质干扰<sup>[13]</sup>,但不适用于熊胆粉此类的以小分子成分占多数的中药材。

以能代表各类别结构类型的15种化合物作为指标,考察优化QuEChERS法各步骤。①提取水相:考察NaOH溶液、Na<sub>2</sub>EDTA-McIlvaine缓冲液和1%醋酸溶液,结果表明必须使用Na<sub>2</sub>EDTA-McIlvaine缓冲液方能将四环素类从水层提取出来;②提取有机相:考察乙腈、5%醋酸乙腈溶液和15%醋酸乙腈溶液的提取效率,结果表明,多数化合物使用5%醋酸乙腈溶液的峰面积稍高;③净化材料:因熊胆粉基质中胆汁酸含量较高,且成分复杂,考察PSA、PAX(强阴离子交换)、GCB(石墨化炭)等多种吸附材料及其比例,最终确定硫酸镁、C18、PSA(1:1:6)作为吸附材料,可最大程度的吸附酸性基质,降低基质效应。

于流动相水相(0.2%甲酸溶液)中加入5 mmol·L<sup>-1</sup>甲酸铵,可缓冲熊胆粉基质的酸性,减少样品中部分化合物保留时间与对照品的差异;加入0.5 mmol·L<sup>-1</sup>氟化铵可极大优化四环素类化合物的峰形。因此流动相水相最终确定为0.2%甲酸(含5 mmol·L<sup>-1</sup>甲酸铵和0.5 mmol·L<sup>-1</sup>氟化铵)溶液。

综上,本研究采用QuEChERS前处理方法,建立了超高效液相色谱串联质谱法定性筛查熊胆粉中169种兽药残留。本文方法为其他动物药材提供了借鉴思路。可以该方法为基础,结合具体基质的特点,从提取方法、净化技术、色谱条件等多个方面进行研究和优化,以尽可能去除干扰和基质效应,将方法扩展应用至不同基质中。比如,本研究团队调整了净化填料,已成功建立了山羊角中173种兽药残留的定性筛查方法,以及药用辅料炼蜜和含炼蜜的中成药中41种兽药残留的定性筛查方法。

由于基质的复杂性,同时建立近两百种化合物的定量测定方法较为困难,部分化合物回收率较低。未来将在定性筛查并初步定量的基础上,进行安全风险评估,针对安全风险较高的兽药品种(如熊胆粉中氧氟沙星、甲硝唑、安替比林和喹乙醇等)建立专属性定量检测方法,并制定合理限度,用标准倒逼源头养殖的规范化,全面控制动物源性中药材的安全性风险。

## References

- [1] Zhan J, Zhong Y, Yu X, et al. Multi-class method for determination of veterinary drug residues and other contaminants in infant formula by ultra performance liquid chromatography-tandem mass spectrometry [J]. Food Chem, 2013, 138: 827-834.
- [2] Li S, Chen SB, Li LQ, et al. System of simultaneous extraction and cleaning of 99 veterinary drugs in food [J]. Chin J Chromatogr (色谱), 2018, 36: 506-517.
- [3] Wang JQ, Ma LL, Cao YH, et al. UPLC-MS/MS high-throughput detection of 56 veterinary drug residues in food products of animal origin [J]. Chin J Anal Lab (分析实验室), 2018, 37: 306-310.
- [4] Hao J, Jiang J, Yu JL, et al. Simultaneous determination of multi-veterinary drug residues in animal-origin food by solid phase extraction coupled with ultra performance liquid chromatography-tandem mass spectrometry [J]. Food Sci (食品科学), 2017, 38: 266-272.
- [5] Fang CR, Gao J, Wang YX, et al. Determination of 125 veterinary drugs residues in eggs by QuEChERS-ultra-high performance liquid chromatography-tandem mass spectrometry [J]. Chin J Chromatogr (色谱), 2018, 36: 1119-1131.
- [6] Qin L, Dong YL, Wang GL, et al. Determination of 42 veterinary drug residues in common animal derived food by dispersive solid phase extraction coupled with liquid chromatography-tandem mass spectrometry [J]. Chin J Chromatogr (色谱), 2018, 36: 880-888.
- [7] Li D, Wang HJ, Zhang YJ, et al. Determination of quinolones residues in egg by QuEChERS and high performance liquid chromatography-fluorescence detection [J]. J Food Saf Qual (食品安全质量检测学报), 2018, 9: 4916-4920.
- [8] Song W, Zhao MY, Han F, et al. Determination of 39 veterinary drug residues in *procambusclarkii* by ultra-high performance liquid chromatography-quadrupole-time of flight mass spectrometry [J]. Chin J Chromatogr (色谱), 2018, 36: 1261-1268.
- [9] Xue H, Jin Y, Yu YL. Simultaneous determination of 33 veterinary drugs in pork by ultra performance liquid chromatography-tandem tripe-quadrupole linear ion trap mass spectrometry [J]. J Anal Sci (分析科学学报), 2018, 34: 387-392.
- [10] Li R, Yang LQ, Zhang PY, et al. Determination of 64 veterinary drug residues in aquatic products by ultra-high performance liquid chromatography-quadrupole/electrostatic field orbitrap high-resolution mass spectrometry [J]. Chin J Chromatogr (色谱), 2017, 35: 1266-1275.
- [11] Wang J, Xiong AZ, Cheng RR, et al. Systematical analysis of multiple components in drainage bear bile powder from different sources [J]. China J Chin Mater Med (中国中药杂志), 2018, 43: 2326-2332.
- [12] Ministry of Agriculture. No. 235 Bulletin of the Ministry of Agriculture of the People's Republic of China [EB/OL]. 2002 [2019-08-20]. [http://www.moa.gov.cn/govpublic/SYJ/201006/t20100606\\_1535491.htm](http://www.moa.gov.cn/govpublic/SYJ/201006/t20100606_1535491.htm).
- [13] Huang ZW, Min YH, Du G, et al. Rapid screening and confirmation of 55 kinds of veterinary drug residues in pork by QuEChERS EMR-Lipid technology and LC/MS/MS [J]. Sci Technol Food Ind (食品工业科技), 2019, 40: 270-276.