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Analytical Methods for Determination of Apigenin - An Update

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ABSTRACT

Apigenin is a flavone abundantly present in various plants such as cherries, broccoli, legumes, parsley, and chamomile. In present article different analytical methods reported in various scientific studies for quantification and detection of apigenin in different formulations are presented. Various databases such as Science Direct, PubMed Medical Subject Headings and Google Scholar were used to retrieve the journal articles. Reported analytical methods for apigenin includes HPLC, UHPLC, HPTLC, TLC, GC, and capillary electrophoresis with MS, UV, PDA, and DAD detection. HPLC- MS was found to be frequently used for apigenin detection.

Keywords: apigenin, analytical method, flavone, chromatography.

INTRODUCTION

Apigenin (APG) is a trihydroxyflavone with molecular formula $C_{15}H_{10}O_5$ and is chemically known as 5,7-dihydroxy-2-(4-hydroxyphenyl) chromen-4-one (fig. 1). APG is widely distributed in various fruits, vegetables, herbs, and spices at significant levels. Major APG containing food sources include thyme, cherries, tea, olives, broccoli, celery, and legumes, with the most abundant sources being the leafy herb parsley (*Petroselinum cripspum*) and dried flowers of chamomile (*Matricaria chamomilla*) (Avallone 2000; Poureini 2020).

APG belongs to BCS class II with poor aqueous solubility and high permeability in the intestine. The solubility of APG in water is 183 mg/L at 25 °C and it is soluble in ethanol and very soluble in dilute alkalies (Shakeel 2017). APG was found to possess a maximum solubility of 2.16 µg/mL at pH 7.4, resulting in low dissolution and poor bioavailability (J. Zhang 2012). Owing to numerous pharmacological effects and lack of review of analytical methods reported in the literature, we reviewed the properties, biological effects and analytical methods for quantitation and detection of APG in the pharmaceutical formulations and different biological matrices.

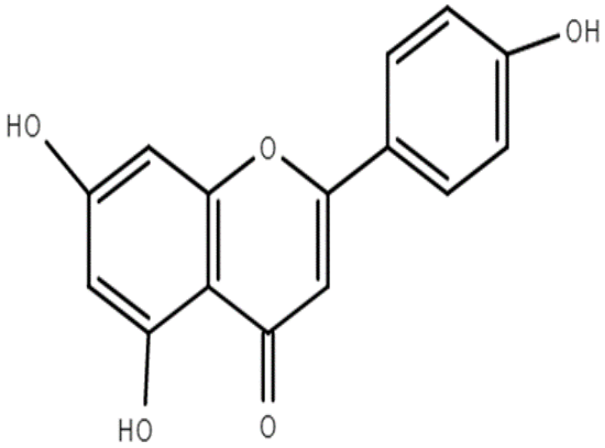

Fig 1. Structure of apigenin.

Pharmacological activities

APG possesses significant antioxidant activity as revealed by different *in vitro* studies. Effects of APG on hydrogen peroxide-induced oxidative cell damage and cellular dysfunction in MC3T3-E1 osteoblastic cells was investigated. Treatment of osteoblastic cells with APG (1 μM) in the presence of H_2O_2, attenuated all the H_2O_2-induced deleterious effects suggested antioxidant protected mitochondrial function in osteoblastic cells (Jung 2014). APG was proven to exhibit significant nephroprotective effect and therapeutic potential for alleviating diabetic nephropathy. Treatment of diabetic rats with APG at 20 mg/kg dose attenuated renal dysfunction, oxidative stress, and decreased fibrosis via suppression of MAPK-NF-κB-TNF-α and TGF-β1-MAPK-fibronectin pathways. Histopathological examination demonstrated reduced inflammation, collagen deposition, and glomerulosclerosis in the renal tissues comparable to that of ramipril standard (Malik 2017). APG is proposed for the therapeutic management of various inflammatory diseases attributed to its anti-inflammatory property. Anti-inflammatory activity of APG involves blocking of nitric oxide-mediated COX-2 expression and monocyte adherence. APG pre-treated RAW 264.7 macrophage cells exhibited inhibition of collagenase activity involved in rheumatoid arthritis and suppression of lipopolysaccharide stimulated production of nitric oxide and expression of COX-2. Moreover, APG profoundly reduced the tumour necrosis factor-α induced adhesion of monocytes to the human umbilical vein endothelial cells monolayer. Moreover, APG significantly suppressed the TNF- α -stimulated upregulation of vascular cellular adhesion molecule-1, intracellular adhesion molecule-1, and E-selectin-mRNA to basal levels (Lee 2007). APG demonstrated significant antibacterial activity in five pathogenic bacterial strains such *Pseudomonas aeruginosa*, *Salmonella typhimurium* (17.36 ± 0.18 mm), *Proteus mirabilis* (19.12 ± 0.01 mm), *Klebsiella pneumoniae*, and *Enterobacter aerogenes*. The MICs for APG against all tested bacterial strains was found to be greater than 4 mg/mL (Nayaka 2014). APG displayed anticancer activity against MDA-MB-231 human breast cancer cell lines and human prostate epithelial RWPE-1 cells with IC_{50} values of 44.44μM, and 10 μM respectively. Mechanism involved in cytotoxicity of APG was proposed to involve decrease in ROS production, thereby abrogating caspase-9/-3 and apoptosis activation (Warkad 2021). APG also exhibited therapeutic activity in the management of hypertension and cardiac hypertrophy by modulating NADPH

oxidase-dependent ROS generation and inflammation in the hypothalamic paraventricular nucleus. APG reduced the depression caused by corticosterone in mice following once-a-day subcutaneous administration (40 mg/kg) of corticosterone for 21 days and 20 and 40 mg/kg administration of APG, 30 min. prior to the corticosterone injection. The behavioural tests indicated that APG reversed the reduction of sucrose preference, the elevation of immobility time, increase in serum corticosterone levels and the decrease in hippocampal brain-derived neurotrophic factor levels (Weng 2016).

METHODOLOGY

Data from various analytical studies available in the literature in the period of 1997 to 2023 was reviewed. Various databases such as Science Direct, Pubmed Medical Subject Headings and Google scholar were used to retrieve the journal articles. Keyword combinations such as "Analytical approach for detection or quantification of APG" or "Chromatography of APG," were used for searching the databases. Publications were manually filtered based on the titles and the abstracts. Duplicate, irrelevant and text not meeting the contributing criteria were excluded from the study. The criteria included the (a) originality of the publication published in peer reviewed journal, (b) identification methods, (c) quantification and detection methods in different formulation and biological matrices, and (d) articles written in English.

Sample preparation techniques

In an analytical method, the choice of sample preparation technique is critical for reducing the effect of matrix interferences and concentrating the analyte. Samples can be processed by various methods such as protein precipitation, liquid liquid extraction, and solid phase extraction. Choice of the method depends on the properties of the sample and the experimental design of the study. The protein precipitation technique involves deproteination of the sample using organic solvents, salt, metal ions, and acids. The metal ions bind to the functional group of proteins and result in deproteination. Organic solvents such as methanol in combination with acetonitrile (Guo 2020; Shen 2019), 0.1 % formic acid (Liuting Wei 2020), and ethyl acetate (Dong 2017) were used in protein precipitation technique. In the liquid-liquid extraction method, the analyte is distributed between immiscible and partially miscible solvents. pH of the aqueous phase should be adjusted to facilitate the migration of non-ionized analyte to the organic phase. Various plant materials such as Chamomile flowers and Chamomile tea, *Ziziphus jujuba* , *Swertia mussotii, Saussurea involucrate, Semen cuscutae*, *Ginkgo biloba* were subjected to liquid liquid extraction using solvents as ethanol: water (50: 50 v/v) (H. Zhang 2019), methanol: acetone (3:1 v/v) (Liuting Wei 2020), ethyl acetate (Guo 2020)(T. Wang 2017),water (X. B. Cui 2015), 80% ethanol (v/v) (Shen 2019) for quantification of APG.

Analytical methods

Various methods described for the detection of APG and its residue in various herbal samples and animal tissues include high performance liquid chromatography (HPLC), ultra-high performance liquid chromatography (UPLC), thin layer chromatography (TLC), high performance thin layer chromatography (HPTLC), capillary Electrophoresis (CE) and gas chromatography (GC). Various detection modes used were ultraviolet detector (UV), diode-array photodiode-array detector (PDA), flame ionization detector (FID), electrochemical detector (ECD), and mass spectrometer (MS). Several articles revealed the UV and MS detection of APG by HPLC using C18 column using various mobile phases at a flow rate of 0.1 to 2 mL/min with either isocratic or gradient elution.

CONCLUSION

APG is a flavonoid present in various fruits, herbs, spices, and vegetables with abundant occurrence in broccoli, tea, cherry, chamomile flower, and parsley. APG showed effective therapeutic properties including antioxidant, anti-hyperglycemic, anti-inflammatory, anti-microbial, cardioprotective, cytotoxicity, anti-atherogenic, and anti-depressant activities. Several analytical methods are reported in the literature for APG analysis in various matrices. According to the literature review, the common analytical technique used is HPLC/MS to analyse the APG from the plant samples for precise detection and separation. Among others various analytical methods based on LC/MS, UHPLC/MS, HPLC/UV, HPLC/PDA, UHPLC/PDA, UHPLC/DAD, and HPTLC are used in the analysis of APG. Additional, methods such as capillary electrophoresis, HPTLC, and electrokinetic chromatography are utilized by researchers for the quantification of APG.

Abbreviation

ROS – reactive oxygen species
MAPK – mitogen activated protein kinase
TNF – tumour necrosis factor
IL – interleukin
DN – diabetic nephropathy
TRBP – transactivation response element RNA binding protein
HUVEC – human umbilical vein endothelial
MIC – minimum inhibition concentration
APG – Apigenin
HPLC – high pressure liquid chromatography
LOQ – limit of qualification
LLOQ – lower limit of qualification
LOD – limit of detection
HPLC – high pressure liquid chromatography
HPTLC – high pressure thin layer chromatography
UV – ultraviolet
MS – mass spectroscopy
DAD – diode array detection
PDA – photodiode array detectors

Declaration

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Table 1. Summary of analytical method for analysis of APG.

Sr. no	Matrix	Method	Detector	Wavelength	Mobile phase	Column Temperature	Stationary phase	Flow rate	LOD and LOQ	Linear range	Ref
1	epidermal cells obtained from SENCAR mice	Reversed -Phase HPLC	UV	212, 269, and 337 nm	0.1% (v/v) trifluoroacetic acid (TFA) in water: acetonitrile (52:48 v/v)		2.1 × 250 mm Alltima C_{18} column	0.3 mL/min.	LOD-1.15 ng	0.225-2.25 µg/mL	(B. Li, Robinson, and Birt 1997)
2	Bile and blood sample	LC-MS/MS	MS	-	0.1% v/v formic acid in water: acetonitrile (1:1 v/v)	45°C	Restek Ultra BPh (5 µm, 100 mm×2.1 mm)	0.45 mL/min	LOQ in bile – 10nM LOQ in blood – 1.56nM	10 nM–5000 nM (bile) and 1.56 nM–4000 nM (blood)	(Tu 2020)
3	Chamomile flowers and Chamomile tea extracts	UHPLC–MS/MS	MS	-	Methanol: 0.1 % v/v formic acid (11.5:88.5 v/v)	30°C	Acquity BEH C_{18} (100×2.1mm, 1.7µm)	0.45 mL/min.	LOQ-5–20 nmol/l	0.02–10µmol/l	(Nováková 2010)
4	*Semen Cuscutae* extract	HPLC-MS/MS	MS	-	0.1% formic acid in water (A) and acetonitrile (B)	30°C	CORTECS C_{18} column (4.6 ×150 mm, 2.7 µm)	0.3 mL/min	LOQ- 1 ng	1–250 ng/mL	(Shen 2019)
5	Mice plasma	LC-MS/MS	MS	-	methanol: acetonitrile (90: 10, v/v) and 0.1% v/v formic acid in 10 mM ammonium formate buffer in the ratio of	40°C	Phenomenex Luna C_{18} (150 x 4.6 mm, 3.0 µm)	1.00 mL/min.	LLOQ - 0.1ng/mL	0.1 – 200 ng/mL	(Cheruvu 2018)

					70: 30 v/v						
6	Mixed samples of Rosmarinic acid, ferulic acid, resveratrol, caffeic acid, APG and luteolin	HPLC	PDA	283 nm	0.1% (v/v) aqueous phosphoric acid: acetonitrile (75:25 v/v)	30°C	A Venusil MP-C_{18} column (4.6 x 250 mm, 5 µm	1.0 mL/min	LOD and LOQ of this method was 0.36 and 0.86 mM	1.2-59.5 µM	(Qi 2017)
7	Natural Dyes	RP - HPLC	UV-Vis Diode Array Detector (DAD)	275 nm	solvent X: H 2 O + 0.1% (v/v) trifluoroacetic acid and solvent Y: acetonitrile + 0.1% (v/v) trifluoroacetic acid	35°C	(Altima C_{18}, 250 mm x 3.0 mm i.d., 5 µm	0.3 mL/min up to 0.5 mL/min	LODs ranging between 0.03 to 0.08 µg/mL and LOQs ranging between 0.09 to 0.24 µg/mL	0.1-2.5 µg/mL	(Vasileiadou, Karapanagiotis, and Zotou 2021)
8	Rat plasma	UFLC–MS/MS	MS	-	0.1% v/v formic acid–water: methanol (50:50 v/v)	30°C	Venusil MP C_{18} chromatographic column (100 mm × 2.1 mm, 3 µm)	0.2 mL/min	LOQ- 1.0 ng/mL	1.00-500.0 ng/mL	(T. Wang 2017)
9	*Ziziphus jujuba* and *Ziziphus nummularia* extract	HPLC-QTOF-MS/MS	MS	-	0.1% v/v formic acid was kept as solvent X while methanol with 0.1% v/v formic acid was kept as solvent Y	40°C	Macherey-Nagel Nucleodur C_{18} column (3.0 mm x 100 mm dimensions and 1.8 µm particle	0.7 mL/min. and 4.0 µL	LOD- 0.06 ng/mL to 4.10 ng/mL LOQ- 0.17 ng/mL to 12.42 ng/mL	01-2000 ng/mL	(Khan 2020)

							size)				
10	Rat Plasma	HPLC-UV	DAD – UV detector	350 nm	methanol and 0.2% phosphoric acid (50: 50, v/v)	25°C	Agilent Eclipse XDB-C_{18} column (250mm × 4.6 mm, 5 µm)	1.0 mL/min	LLOQ - 0.11 µg/mL	0.11–10.60 µg/mL	(Dong 2017)
11	Samples collected in stagnant water bodies domin.ated by different cyanobacterial species	LC-MS/MS	MS	-	Water (solvent X) and acetonitrile (solvent Y)	-	Waters Acquity UPLC BEH C_{18}, 50 x 2.1 mm, with 1.7 µm particles and with guard column VanGuard C_{-18}	0.4 mL/min.	-	0.05 – 100 ng/mL	(Procházková 2017)
12	Rat Plasma and Liver Tissue Samples	LC-MS/MS	MS	-	(A) 0.01% v/v formic acid and (B) 0.01% v/v formic acid in methanol	indoor temperature	ACQUITY UPLC BEH-C_{18} (1.7 µm, 2.1 × 50 mm)	0.3 mL/min.	LLOQ 1.0 ng/mL	1.00–200 ng/mL	(Y. Li 2019)
13	Herbal preaparation	capillary zone electrophoresis	UV	238nm	0.5 M NaOH for 10 min., distilled water for 10 min.	-	Uncoated silica separation capillaries of 53 cm (44.2 cm effective length) ×75 µmID×375 µm OD	-	LOD- 2.7 µg/mL	5-550 µg/mL	(Lü 2012)

14	12 compounds in BPYQ	UHPLC-ESI-MS/MS	MS	-	acetonitrile and 0.1% (v/v) formic acid aqueous solution	30°C	Poroshell 120 SB-Aq column (50 × 2.1 mm, 1.7 µm)	0.4 mL/min	LOD-1.02ng/mL, LOQ-3.47ng/mL	10.2–0.15 µg/mL	(Q. Xie 2021)
15	*Cotula cinerea* extracts	HPLC/QTOF-MS analysis	QTOF-MS	-	(A) a stepwise gradient of water containing methanol 20% with 5 mM formate and 0.1% v/v formic acid, and (B) methanol containing water 10% with 5 mM formate and 0.1% v/v formic acid	30°C	Inertsil ODS-4 column (3 µm, 150x2.1 mm i.d)	0.4 mL/min.	-	-	(Guaoguuaou 2020)
16	Botanical raw material extract	UHPLC-PDA-MS	PDA	335nm	acetonitrile and acidified water with 0.1% v/v formic acid	28°C	C18 (50 × 2.1 mm, 1.7 µm) column	0.35 mL/min.	LOD- 2.87 LOQ- 8.70	0.9765 – 500.00 µg/mL	(Kim 2021)
17	Rat plasma	UPLC-MS/MS	MS	-	0.1% v/v formic acid aqueous solution and acetonitrile	35°C	Acquity UPLC® BEH C_{18} column (2.1 × 50 mm, 1.7 µm	0.2 mL/min.	LOQ- 3 ng/mL	-	(Lan Wei 2016)
18	Food analysis	RP-UHPLC	Electrospray ionization	-	Water: methanol (90:10 v/v), and 5 mM	30°C	Acclaim RSLC C_{18} column (2.1 mm×	0.2-0.4 mL/min.	LOD-0.015 µg/mL LOQ-	-	(Kalogiouri 2016)

			quadrupole time of flight tandem mass spectrometry- try		ammonium acetate (Solvent X), and 100 % methanol and 5 mM ammonium acetate (solvent Y)		100 mm, 2.2 µm)		0.046µg/mL		
19	Rat plasma	UHPLC–MS/MS	MS	-	0.1% v/v formic acid aqueous solution and acetonitrile	-	Agilent ZORBAX RRHD Eclipse Plus C_{18} column (2.1 mm × 50 mm, 1.8 µm)	0.3 mL/min.	LLOQ- 2.0 ng/mL	-	(Tian 2017)
20	Rat plasma	LC-MS/MS	MS	-	acetonitrile: methanol: water (35:40:60 v/v/v)	25°C	Luna C_{18} (5 µm, 100mm×2.0 mm)	0.2 mL/min	LLOQ- 2.5 ng/mL	2.5–5000 ng/mL	(Wan 2007)
21	Human plasma	UPLC-MS/MS	PDA	-	acetic acid 0.2% v/v as solvent X and acetonitrile as solvent Y.	30°C	BEH C_{18} column (1.7µm, 100mm×2.1mm i.d.)	0.4 mL/min	LOD- 0.007 µM LOQ- 0.02 µM	0.02–2µM	(Suárez 2009)
22	Polyphenols in royal jelly products	LC-Exactive-Orbitrap analyzer	MS	-	50:50 v/v acetate ammonium 30 mM, pH 5 and MeOH	30°C	Acquity C_{18} column (2.1 mm × 100 mm, 1.7 µm particle size)	0.2 mL/min.	LOQ- 10 to 150 µg/kg	2 to 2000 µg/L	(López-Gutiérrez 2014)
23	Flavonoids in environmental water samples	HPLC	PDA	360 nm	(Methanol:Acetonitrile: 0.02 M H3PO4	25°C	ZORBAX Bonus-RP analytical	1.0 mL/min.	LOD- 0.11 µg/L LOQ- 0.35	0.35–750 µg/L	(Y. Liu 2016)

					(35:35:30 v/v/v)		column 15 (25 cm long × 4.6 mm i.d.)		µg/L		
24	*Swertia mussotii* extract	capillary zone electrophoresis (CZE)	UV	250 nm	-	20°C	capillary of 68.5 cm×75 µm i.d. with an effective length of 60.0 cm	-	LOD- 0.2538 µg/mL LOQ- 0.5076 µg/mL	8.8 – 133.3 µg/mL	(Gao 2015)
25	Rats	UHPLC–MS/MS	MS	-	0.1% v/v acetic acid water (solvent X) and methanol (solvent Y)	25°C	Agilent ZORBAX RRHD Eclipse Plus C_{18} column (2.1 mm × 50 mm, 1.8 µm)	0.3 mL/min.	LLOQ- 1.5 mg/mL	1.5–500 ng/mL	(X. Chen 2018)
26	plasma and tissues of rats	HPTLC	-	268 nm	n-hexane:ethyl acetate:glacial acetic acid, (5:3:1 v/v/v) and toluene:methanol:formic acid, (8:2:0.2 v/v/ v)	-	precoated silica gel 60 F254 alumin.um -coated TLC plates (20 cm × 10 cm)	-	LOD 5.22 ng/band, LOQ 15.84 ng/band	20-120 ng/band	(Sadhana, Lohidasan, and Mahadik 2017)
27	Rat	UPLC-MS/MS	MS	-	0.1% v/v formic acid in water (A) and 0.1% v/v formic acid in acetonitrile (B)	35°C	Acquity UPLC HSS T3 column (2.1 × 100mm, 1.8 µm)	0.4 mL/min.	LLOQ- 0.2 ng/mL	0.2–100 ng/mL	(Y. Wang 2020)
28	extracts from	UHPLC	PDA	330 nm	solvent X:	25°C	Acquity	0.35	LOD- 0.04	0.1 –	(Nalewaj

	inflorescences of *Cirsium vulgare* (Savi) Ten				0.1% v/v formic acid in water, solvent Y: 0.1% v/v formic acid in acetonitrile and solvent C: 100% methanol		UPLC BEH C_{18} column (130 Å, 1.7 µm, 2.1 mm × 100 mm)	mL/ min.	µg/mL	100 µg/mL	ko-Sieliwoniuk 2017a)
29	Rat plasma	UPLC-MS/MS	MS	-	acetonitrile: water (70: 30 v/v), each with 0.1 % v/v formic acid	45°C	Acquity UPLC BEH C_{18} analytical column (100 ×1.0 mm, i.d., 1.7 µm particle size)	0.2 mL/min	LLOQ-0.5 ng/mL LLOD-0.3 ng/mL	0.5-200 ng/mL	(Maher 2017)
30	olive oil polyphenols	HPLC-DAD/MS/MS	DAD and MSD	338 nm	water with 0.1% v/v formic acid (A) and methanol:isopropylalcohol (90:10 v/v) with 0.1 % v/v formic acid (B)	35°C	Synergi Polar (250 X 4.6 mm, 4 µm)	1 mL/min	LOD-0.029 mg/kg LOQ – 0.096 mg/kg	0.4-18.8 mg/kg	
31	Phytochemicals in Achillea species	LC-MS/MS	MS	-	eluent A (water, 10 mM ammonium formate and 0.1% v/v formic acid) and eluent B (acetonitrile)	35°C	RP-C_{18} Inertsil ODS-4 (100 mm×2,1 mm, 2 µm)	0.25 mL/min	LOD-5.4 µg/L LOQ-6.3 µg/L	25-1000 µg/L	(Yilmaz 2018)
32	Rat plasma	LC-	MS	-	methanol (A)	30°C	Diamonsil	0.8	LLOQ -	1.70–	(Sun

		MS/MS			and 0.1% v/v acetic acid (B)		C_{18} column (150 mm × 4.6 mm, 5 m)	0.1% Xcetic acid /min.	1.70 ng/mL	1088.00 ng/mL	2013)
33	traditional Chinese medicine of antitussive	LC–MS-MS	MS	-	0.1% v/v acetic acid (A) and methanol (MeOH) containing 0.1% v/v acetic acid (B)	40°C	Acquity UPLC® HSS C_{18} (2.1 × 150 mm, 1.8 µm)	0.2 mL/min.	LOD-0.500 ng/mL LOQ-1.000 ng/mL	8–512 ng/mL	(G. Liu 2016)
34	Honey	HPLC-MS/MS	MS	-	Methanol	-	ODS-3 column (150 mm×4.6 mm, 3 µm)	-	LOD- 20 µg/kg	0-200 µg/kg	(Jianbo Hou 2020)
35	essential oils and extracts	HPLC	DAD	325 nm	Solvents A (water with acetic, o-phosphoric or trifluoroacetic acid as modifier) and B (methanol and ACN as organic modifiers)	35 °C	ZORBAX Eclipse XDB-C_{18} (4.6×150mm,5 µm)	1 mL/min.	LOD - 1.13mg/kg	10–1300 mg/kg	(Stashenko 2013)
	essential oils and extracts	GC	Flame ionization detection (FID)	-	-	295°C	A fused-silica capillary column DB-5MS (60 m × 0.25 mm id) coated with 5% phenyl	1 mL/min	4.6 mg/kg	10–1300 mg/kg	(Stashenko 2013)

							poly(methylsiloxane) (0.25-µm film thickness)				
36	rice	RP-HPLC	PDA	360nm	Solvent(A) acetonitrile, Solvent(B) methanol and Solvent(C) 0.5% (v/v) acetic acid in water	25°C	PerfectSil Target ODS-3 (250 mm × 4.6 mm, 3 µm)	1 mL/min.	LOD^{-1}.07 µg/g LOQ- 3.25 µg/g	1.6–32.0 µg/g	(Irakli 2012)
37	Rats	LC-MS/MS	MS	-	methanol-water (60:40, v/v)	30°C	Eclipse XDB-C_{18} column (50×2.1 mm, 1.8 µm	0.25 mL/min.	LLOQ-0.845 ng/mL	0.845–845 ng/mL	(Zhou, Li, and Yan 2018)
38	Leaves of various plant extract	HPLC-UV	UV	253 nm	Mobile phase A was water with acetic acid (pH 2.94) and Mobile phase B was acetonitrile	25°C	LiChrospher R RP-$_{18}$ (5 µm) 250 × 3 mm column	1 mL/min.	LOD- 24.4 ng/mL LOQ- 81.3 ng/mL	-	(Bajerová 2014)
39	Antioxidant compounds of propolis	CE-ESI-MS	MS	-	-	-	Fused-silica capillary of 50 lm,.id	4.6 l L/min.	-	-	(Gómez-Romero 2007)
40	Herbal product	HPLC-DAD-ESI-MSD	DAD	335 nm	mobile phase consisted of A = acetonitrile and B = formic acid 0.05% v/v (aqueous)	40°C	Zorbax Eclipse XDB-C_8, 150 × 3.0 mm, particle size 3.5 micron	0.5 mL/min.	LOD - 1.29 µg/mL LOQ - 4.30 µg/mL	-	(Saleem 2009)

41	Rat plasma	UPLC-ESI-MS/MS	MS	-	0.1% v/v formic acid aqueous solution (A) and methanol (B)	40°C	Acquity UPLC BEH C18 column (100 × 2.1 mm, i.d., 1.7 µm)	0.2 mL/min.	LLOQ-2.38 ng/mL	2.38–228.6 ng/mL	(X. B. Cui 2015)
42	*Scutellaria indica* L extract	UHPLC–QTOF–MS	MS	-	0.1% v/v formic acid–water (A) and acetonitrile (B)	35°C	ACQUITY BEH C_{18} column (100 mm × 2.1 mm, 1.7 mm)	0.40 mL/min	LOD-10.52 ng/mL LOQ-16.24 ng/mL	0.50–5.00 µg/mL	(He 2016)
43	*Perilla frutescens* L extract	Capillary electrophoresis	electrochemical detection	-	-	-	75 cm length, 25 µm i.d., and 360 µm o.d. fused silica capillary	-	LOD- 2 × 10^{-7} g/ mL LOQ- 5 × 10^{-7} g/ mL	1−1000 µg/mL	(Peng, Ye, and Kong 2005)
44	Sideritis species, herbal extracts, green tea, black tea, and coffee	HPLC	PDA	330 nm	methanol–ACN (95:5 v/v) (A) and acetic acid 0.01% v/v (B)	Room temp	ODS-3 HD 5-µm analytical column (250 mm x 4.6 mm id)	0.8 mL/min	LOD- 2.0 mg/L LOQ-0.7mg/L	-	(Samanidou, Tsagiannidis, and Sarakatsianos 2012)
45	*Scutellariae Barbatae* Herba extract	capillary zone electrophoresis	DAD	214 nm	-	25°C	fused-silica capillary tube with size 50 mm (I.D.) x 60.2 cm (50 cm active length)	-	LOD- 0.17 µg/mL LOQ- 0.53 µg/mL	1.70–136 mg/mL	(Y. Y. Li 2013)
46	*Saussurea*	LC-ESI-	Ion trap	-	Solvent X	25°C	Reversed	0.8	LOD - 2.4	5.0–	(Xu

	involucrata extract	MS	as mass analyser		(methanol) and solvent Y (HPLC grade water acidified to pH 3.0 with trifluoroacetic acid)		phase C_{18} analytical column of 250mm x 4.6mm and 5 mm particle size	mL/min.	x 10^{-4} mg/mL	25mg/mL	2009)
47	*Wikstroemia indica* (L.) extract	HPLC	electrospray ionization tandem mass spectrometry	-	0.05% v/v formic acid aqueous solution (A) and acetonitrile (B)	30°C	ACQUITY UPLC® BEH C_{18} column (2.1 × 50mm, 1.7µm)	0.2 mL/min.	LOD- 3.805 ng/mL and LOQ- 12.38 ng/mL	0.1104-2.6496 µg/mL	(Lan Wei 2015)
48	*S. tormin.alis, S. aucuparia, S. domestica* extract	HPLC	PDA	340 nm	solvent X (water–85% orthophospho-ric acid, 100:0.5, v/w, pH 2.0), solvent Y (ACN), and sol- vent C (THF)	30°C	C_{18}-silica column (Ascentis® Express, 4.6 mm × 150 mm, 2.7 µm)	1 mL/min	LOD- 0.026 µg/mL	0.10–41.28 µg/mL	(Olszewska 2012)
49	*Erigeron breviscapus* (Vant.) extract	high-performance capillary electrophoresis	electrochemical detection (ED)	-	-	-	75 cm length of 25µm i.d. and 360µm o.d. fused silica capillary	-	LOD- 3.2 g/ mL	1×10^{-6} to 1×10^{-4} g/ mL	(Chu 2005)
50	Chinese medicinal preparation SuoQuan formulae	UFLC-MS/MS	Tandem mass spectrometry	-	H_2O containing 0.1% v/v formic acid for solvent X, and methanol	40°C	Shim-pack XR-ODS column (2.0 mm i.d × 100 mm)	0.3 mL/min.	LOD- 2 ng/mL and LOQ- 5 ng/mL	5.0–2000 ng/mL	(F. Chen 2013)

					containing 0.1% v/v formic acid for solvent Y.						
51	*Rumexnervosus Vahl* leaves and stems extract	LC–ESI-MS/MS	MS	-	A (0.1% v/v formic acid) and B (100% methanol)	-	Cosmosil C_{18} column and	0.5 mL/min	LODs - 0.68–1.61 mg/mL and LOQs - 2.27–5.38 mg/L	1-1000 mg/L	(Desta 2016)
52	Rat plasma	UFLC	MS (ESI)	-	A (0.1% v/v formic acid aqueous solution) and eluent B (ACN)	40°C	Waters Acquity UPLC HSS T3 column (2.1 mm × 100 mm, 1.8 μm)	0.3 mL/min	LLOQ-0.25 ng/mL	0.25-0.50 ng/mL	(Guo 2020)
53	Rat plasma and tissues	UHPLC-MS/MS	MS (ESI)	-	water (0.1% v/v formic acid, A) and methanol (B)	25°C	ZORBAX RRHD Eclipse Plus C_{18} column (2.1 × 50 mm, 1.8 μm, Agilent Co.)	0.3mL/min	LOQ- 0.5 ng/mL	0.5–500 ng/mL	(Liuting Wei 2020)
54	*Verbena officinalis* (Verbenaceae) extracts	UHPSFC	Diode array detector	350nm	CO2 (A) and 0.15% v/v phosphoric acid in methanol (B)	30°C	Acquity UPC^2 Torus Diol 1.7 μm column (3.0 x 100 mm, Waters)	1.60 mL/min	APG7-O-glucuronide LOD-1.3μg/mL LOQ-3.8μg/mL APG-7-O-diglucuronide LOD-	APG7-O-glucuronide 6.5–921.0 mg/mL APG-7-O-diglucu	(Gibitz-Eisath 2020)

									0.8 µg/mL LOQ- 2.3 µg/mL	ronide 5.8–897.3 mg/mL	
55	Walnut by products	HPLC-DAD	DAD	280-400nm	(A) 1% v/v acetic acid in water, and (B) ACN	30°C	C_{18} UniverSil column (250 mm × 4.6 mm, 5 µm)	1 mL/min.	LOD- 0.29 LOQ- 0.87 µg/g	1–10 µg/g	(Kalogiouri and Samanidou 2021)
56	Pericarp and Seed of *Alpinia oxyphylla* Capsular Fruit	UFLC-MS/MS	MS	-	water containing 0.1% v/v formic acid as solvent X, and methanol containing 0.1% v/v formic acid as solvent Y	40°C	Phenomenex Synergi Fusion-RP column (4 µm, 2.00 mm i.d. × 50 mm) and Phenomenex Luna C_{18} column (5 µm, 2.0 mm i.d. × 50 mm)	1 mL/min	LOD - 0.10–5.83 ng/mL and LOQ - 1.0–11.7 ng/mL	-	(F. Chen 2014)
57	*Turnera diffusa* extract	UHPLC-DAD	DAD	210 nm, 254 nm, and 280 nm	0.1% formic acid in water (solvent X) and Methanol (Solvent Y)	30°C	Luna Omega 1.6 µm C_{18} 100 Å 100 × 2.1 mm	0.2 mL/min	LOD- 1.39 LOQ- 4.60 µg/mL	5 - 50 µg/mL	(Willer 2019)
58	*Eccoilopus formosanus* extract	HPLC-ESI-MS	ESI-MS	-	0.1% v/v formic acid aqueous solution (solution A) and acetonitrile (solution B)	40°C	RP-C_{18} column (XBridge BEH 2.5 µm, 150 mm × 3 mm)	0.3 mL/min.	LOQ 0.5 µg/mL	1–50 µg/mL	(Ho-Shin Huang 2020)

59	*Lychnophora salicifolia*	HPLC	DAD	254 and 300 nm	water (A) and acetonitrile (B)	Room temp	Nucleodur Macherey-Nagel C_{18} gravity, 3 µm (70 mm × 4.0 mm)	0.3 mL/min	-	-	(Gouvea 2014)
60	*Asparagus officinalis* roots extract	UPLC	DAD	278 nm	acetonitrile and 0.1% v/v formic acid in methanol-water	30°C	Hypersil GOLD aQ column (250.0 mm × 4.6 mm, particle size 5 µm)	0.25 mL/min	LOD- 10 ng/mL LOQ-30 ng/mL	30–500 ng/mL	(H. Zhang 2019)
61	*Roscoea purpurea* Tubers extract	RP-HPLC	PDA	285nm	0.1% v/v formic acid in water (A) and pure acetonitrile (B)	27°C	Supelco C_{18} column (4.6 mm × 50 mm, 5.0 µm,)	0.90 mL/min	LOD- 0.028 µg LOQ- 0.094 µg	0.25–2.0 µg	(Sharad Srivastava 2015)
62	*Matricaria chamomilla* extract	UPLC	PDA	340 nm	4% v/v aqueous acetic acid (eluent A) and acetonitrile (eluent B)	25°C	C_{18} column (150 mm × 2 mm, 1.8 µm)	0.4 mL/min	LOD- 33 ng/mL LOQ- 1000ng/mL	5-50 µg/mL	(G Haghi 2014)
63	Dan Deng Tong Nao Capsules	HPLC-MS/MS	MS	-	A: methanol/acetonitrile (50 : 50 v/v) and B: water containing 0.1% v/v formic acid	45°C	Waters Xbridge™ C_{18} column (4.6mm × 150mm, 3.5 µm particle size)	0.8 mL/min	LOD- 0.6 ng/mL LOQ- 2.0 ng/mL	4.38 - 70.0 ng/mL	(Wu 2014)
64	Chicken	LC-MS	MS	-	0.2% v/v formic acid in water and	-	NUCLEODUR C_{18} Gravity, 3	0.6 mL/min	LOQ- 0.25 µg/mL	-	(Pop 2019)

					methanol		µm, 150 × 3 mm				
65	Leaves of *Clinacanthus nutans*	HPLC-UV/DAD	DAD	330 nm	water with 0.8% v/v glacial acetic acid (solvent X) and acetonitrile (solvent Y)	40°C	Kinetex PFP column (250 × 4.6 mm, 5 µm)	0.7 mL/min	LOD – 0.2 µg/mL and LOQ 0.6 µg/mL	0.4–200 µg/mL	(Chelyn 2014)
66	*Premna mucronata* Roxb	HPTLC	Densitometric absorbance-reflection	366 nm	toluene : ethyl acetate : formic acid (6 :4:0.3 v/v/v)	22°C	Precoated silica gel 60 F254 aluminium plates (20 × 10 cm, 100 µm thick)	-	LOD- 7.97 LOQ- 24.155 ng/band	50 to 250 ng/band	(Patel 2015)
67	Chamomile(Matricaria recutita)	RP-HPLC-DAD	DAD	335nm	water acidified with 0.05% of acetic acid, (Phase A) and acetonitrile (Phase B)	44°C	ShimPack CLC-ODS (C_{18}) analytical column (250mm × 4.6 i.d. and a particle size of 5 µm)	1mL/min	-	24-36 µg/mL	(Miguel 2015)
68	Yixin Badiranjibuya Granules	RP-HPLC-UV	DAD	330 nm	A (water with 0.5% v/v formic acid) and B (acetonitrile)	35°C	Purospher STAR C_{18} column (250mm × 4.6 mm, 5 µm)	1.0 mL/min	LOD-0.1165 LOQ-0.3599 µg/mL	0.1165-34.95 µg/mL	(Yu 2015)
69	Herbs	Electrokinetic chromatography	UV	390 nm	0.03mol/L pH 10.2 sodium tetraborate, 0.01mol/L sodium	35°C	Fused silica capilliary with sized 50µm ID	-	LOD-0.48 LOQ- 0.92 µmol/L	1.0–100 µmol/L	(Głowacki 2016)

					dodecyl sulfate (SDS), and 10% MeCN		x60cm				
70	*Apium graveolens* Seeds extract	GC-TOF-MS and UHPLC-MS/MS	MS	-	5% diphenyl cross-linked with 95% dimethylpolysiloxane (30m× 250 µm, 0.25 µm; J&W Scientific)	-	-	1mL/min	-	-	(Qiao 2020)
71	*Flos Chrysanthemi* Extract in Rats plasma	UPLC-MS/MS	MS	-	0.1% v/v formic acid in water (A) and acetonitrile (B)	20℃	ACQUITY UPLC BEH C_{18} (2.1 × 100mm, 1.7 µm)	0.3 mL/min	LLOQ- 0.2 ng/mL	5.0-1000.0 ng/mL	(Jia 2020)
72	Rat Plasma	UPLC-MS/MS	MS	-	0.1% v/v formic acid in water (A) and ace- tonitrile (B)	20℃	ACQUITY UPLC® CSHTM Phenyl-Hexyl (2:1 × 100mm, 1.7 µm)	0.3 mL/min	LOQ- 0.4 ng/mL	0.4-100 ng/mL	(Fan 2020)
73	Extract of the traditional medicinal herb *Artabotrys hexapetalus*	HPTLC	UV	254 nm	toluene: ethyl acetate: formic acid, 6.5:3:0.5, v/v/v)	25±2℃	Silica gel 60 F254 HPTLC plate (4 cm × 10 cm, 20 mm thickness	-	LOD-13.78 ng/spot LOQ-45.94 ng/spot	100-2000 ng/spot	(Sakshi Bajaj 2018)
74	Rat plasma	UPLC/MS/MS	MS	-	5 mM ammonium acetate aqueous solution (A) and	40℃	ACQUITY UPLC BEH Symmetry Shield RP-$_{18}$ column	0.3 mL/min	LLOQ-0.49 ng/mL	0.49–2000 ng/mL	(W. Y. Chen 2017)

					acetonitrile (B)		(1.7 µm, 2.1 mm × 100 mm)				
75	Rat plasma and tissues	UPLC–MS/MS	MS	-	0.05% v/v acetic acid in water (A) and ACN (B)	40°C	ACQUITY UPLC HSS T3 column (2.1 × 100 mm, 1.8 µm, Waters)	0.3 mL/min	-	0.05-500 ng/mL	(Du 2018)
76	Rat plasma	UPLC-QqQ-MS	MS	-	0.1% formic acid solution (A) and methanol (B)	40°C	C_{18} column (Agilent, USA,2.1mm×100 mm, 1.8 µm)	0.3 mL/min	LLOQ-0.20 ng/mL	0.20-25.82 ng/mL	(Zhuang 2019)
77	Lophatherum gracile Brongn	HPLC-DAD	DAD	330 nm	A (water–acetic acid, 100 : 0.1, v/v) and B (acetonitrile)	35°C	Cosmosil MS-II C_{18} column (250 x 4.6 mm, 5 mm)	1.0 mL/min	LOD- 0.13 µg/mL LOQ- 0.56 µg/mL	1.22–61.29 µg/mL	(Q. Tang 2015)
78	Wine-Processed *Radix scutellariae* extract	UHPLC	PDA	275 nm	formic acid (0.01%, v/v) (A) and methanol (B)	35°C	UHPLC BEH C_{18} column (100 mm× 2.1 mm, 1.7 µm)	0.2 mL/min	LOD- 0.18 µg/mL LOQ- 0.55 µg/mL	7.1–114 µg/mL	(X. Cui 2016)
79	*Commelina communis* extract	UHPLC–Q-TOF-MS-MS	MS	-	0.1% v/v formic acid (A) and acetonitrile (B)	25°C	Poroshell 120 SB-C_{18} (2.1mm × 100 mm, 2.7 µm)	0.3mL/min	LOD-0.00685 ng/mL LOQ-0.0264 ng/mL	0.0003595–0.05750 µg/mL	(X. Zhang 2018)
80	Plant extracts	HPLC	UV	290nm	-	25°C	fused-silica capillary,	-	LOD-0.029 mg/mL	-	(Boiteux 2014)

							57 cm full length, 50 cm effective length, 75 µm id		LOQ-0.096 mg/mL		
81	Rats plasma	HPLC	VWD	350 nm	0.1% formic acid: acetonitrile: methanol (60:16:24, v/v/v)	31±1℃	Agilent Zorbax SB-C_{18} column (250 mm×4.6 mm, 5 µm)	1 mL/min	LLOQ-0.025 µg/mL	0.0250 to 10.0 µg/mL	(Z. Chen 2012)
82	*Lippia alba* extract	HPLC-DAD-ESI-MS	DAD	240, 254, 325 and 350 nm	0.02% (v v−1) tri-fluoroacetic acid (TFA) in water (solvent X) and MeOH/CH3CN 3:7 v/v (solvent Y)	45℃	YMC – Pack Pro C_{18} 150×4.6 mm ID S-3 µm, 12nm	0.9 mL/min	LOD- 0.01 mg/mL LOQ-0.025 mg/mL	0.90–0.010 mg/mL	(Gomes 2019)
83	Er-Zhi-Wan Herbal Medicinal Product	UPLC	UV	220 nm	acetonitrile (A) and 0.1% v/v formic acid (B)	35℃	BEH Shield PR_{18} column (2.1×100 mm, 1.7 µm)	0.3 mL/min	-	0.43–22.2 µg/mL	(M Wang 2015)
84	*Rhamnus davurica* extract	HPLC-ESI-MS/MS	ESI-MS	360 nm	A (0.1% v/v formic acid-H2O), and solvent Y (acetonitrile)	30℃	A reverse C_{18} column (4.6 mm × 250 mm, 5.0 µm)	0.6 mL/min	-	-	(G. Chen and Guo 2017)
85	Table olive polyphenols	UPLC	MS	-	Milli-Q water with 0.025% Xcetic acid	30℃	Zorbax Eclipse XDB-C_{18}	0.8 mL/min	LOD-0.0003 µM	0.010-2.5 µM	(Moreno-González, Juan,

					(phase A) and acetonitrile with 5% Xcetone (phase B)		column (150 mm × 4.6 mm, 5 µm)		LOQ-0.0010 µM		and Planas 2020)
86	polyphenolic components	HPLC	DAD	250 nm	A (0.05% phosphoric acid aqueous solution v/v) and solvent Y (acetonitrile)	50℃	Elite SinoChrom ODS-AP column (250 mm×4.6 mm i.d. with 5.0 µm particle size)	1.0 mL/min	LOD-0.0126 µg/mL LOQ-0.0455 µg/mL	0.46–4.60 µg/mL	(Fang 2014)
87	Chamomiles extract	HPTLC	densitometric reflection /absorption	-	dichloromethane/acetonitrile/ethyl for-mate/glacial acetic acid/formic acid (11:2.5:3:1.25:1.25 v/v/v/v/v)	RT	amino silica	-	LOD- 10 ng/band LOQ-30 ng/band	30-120 ng/band	(Sagi 2014)
88	Ocimum genus extrat	RP-HPLC	PDA	210 and 340 nm	A (0.1% v/v o-phosphoric acid in water) and solvent Y (acetonitrile)	30℃	Phenomenex Luna C_{18} (2) 100Ă column (4.6 X 250 mm, 5.0 µm particle size)	1 mL/min	LOD-0.035 µg/mL LOQ-0.106 µg/mL	0.1-10 µg/mL	(Girme 2021)
89	Dried Flowers of *Matricaria chamomilla* extract	HPLC	DAD	335 nm	0.1% (v/v) acetic acid and solvent Y was acetonitrile	-	C_{18} column (250 × 4.6 mm id, 5 µm particle	1.0 mL/min	LOD-0.090 µg/mL LOQ-	14.4-144 µg/mL	(X. Y. Xie, Chen, and Shi

							size)		0.378 µg/mL		2014)
90	Urine	HPLC-ESI-MS/MS	MS	-	(A) 1% Xqueous formic acid (v/v) and (B) methano	38°C	XDB-Eclipse C_{18} (150 mm × 4.6 mm, 5 µm)	0.4 mL/min	-	0.1−250 µmol/L	(Petreska Stanoeva and Stefova 2013)
91	Rat plasma	HPLC	MS	-	(A) water and (B) MeOH with 0.00075% v/v formic acid	30°C	poroshell 120 SB C_{18} column (2.7 µm, 2.1 mm × 50 mm)	0.24 mL/min	LLOQ-1.37 pg	0.328–168 ng/mL	(Zheng 2014)
92	Rat intestinal bacteria matrix	HPLC-MS/MS	MS	-	methanol (solution A) and 0.1% formic acid in water (solu-tion B)	35°C	Kromasil-C_{18} (4.6 mm × 250 mm i.d., 5.0 µm)	1 mL/min	LOD- 0.07 LOQ- 0.17 µg/mL	0.24–15.23 µg/mL	(D. Tang 2014)
93	Hemistepta lyrata extract	HPLC	UV	254 nm	Solvent X was H2O with 0.05%-trifluoroacetic acid (TFA), solvent Y was methanol: acetonitrile (60:40 v/v)	40°C	Shiseido Capcell PAK C_{18} column (5 µm, 4.6 mm × 250 mm)	1.0 mL/min	LOD- 0.11 LOQ- 0.35 µg/mL	1.56–50.00 µg/mL	(Nugroho 2013)
94	Chamomile flower	HPTLC	TLC scanner 3	340 nm	Ethyl acetate-formic acid-acetic acid-water (30:1:5:1:5:3, v/v/v/v)	-	20cm x 10cm glass HPTLC plates coated with silica gel 60 NH2 F254S	-	-	25-50 ng/spot	(Guzelmeric, Vovk, and Yesilada 2015)
95	Rat plasma	HPLC–	MS	-	A (2 mM	-	ZORBAX	0.9	LLOD-	5.13–	(Dai

		MS/MS			aqueous ammonium acetate) and B (acetonitrile)		SB-Aq (5 µm; 150 mm × 4.6 mm)	mL/min	3.08 and LLOQ- 5.13 ng/mL	513 ng/mL	2015)
96	raw and vinegar-processed Daphne genkwa extract	UHPLC–MS/MS	MS	-	A (0.1% v/v formic acid) and B (0.1% v/v formic acid in acetonitrile)	-	BEH C_{18} column (2.1 mm×50 mm, 1.7 µm)	0.30 mL/min	LLOQ- 3.0 ng/mL	3.0–3000 ng/mL	(Tao 2018)
97	Plasma sample	UHPLC-MS/MS	MS	-	Acetonitrile: 0.1% v/v formic acid (35:65 v/v)	40°C	BEH C_{18} column (50 mm x 2.1 mm, 1.7 µm i.d.)	0.25 mL/mL	LOD- 7.30 ng/mL LOQ- 22.77 ng/mL	5-1000 ng/mL	(Elzayat 2019)
98	Callicarpa herbs	HPLC-DAD-ESI-Trap MS	UV	280 nm	methanol (A) and 0.2% v/v formic acid solution (B)	40°C	Merges C_{18} column (250 mm × 4.6 mm, 5 µm)	1.0 mL/min	LOD- 10 ng/mL LOQ- 26 ng/mL	0.106–10.6 µg/mL	(Shi 2013)
99	Rat plasma	LC–MS/MS	MS	-	methanol (A) and 0.1% v/v formic acid aqueous solution (B) using	25°C	Diamonsil C_{18} column (150 mm x 4.6mm, 5 µm)	0.8 mL/min	LLOQ- 1.00 LOD- 0.28ng/mL	1.00–500.00 ng/mL	(Z. Zhang 2014)
100	Rat plasma	LC–MS/MS	MS	-	Acetonitrile:10 mM ammonium acetate (60:40, v/v)	40°C	Zorbax SB-C_{18} column (150 mm × 4.6 mm, 5 µm)	1.0 mL/min	LOD – 2 ng/mL LLOQ- 10 ng/mL	10–3000 ng/mL	(Yin 2013)