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Perferidone- A review on analytical methods

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ABSTRACT

Pirfenidone is an agent used for the treatment of idiopathic pulmonary fibrosis (IPF). Itis a broad-spectrum antifibrotic medicine was approved in 2014 by USFDA.This review focuses on recent advances in analytical methods for determination of Pirferidone alone or in combination with other medications in pharmaceutical preparations and biological fluids. The analytical techniques UV spectroscopy, high performance liquid chromatography (HPLC), ultra performance liquid chromatography (UPLC), high performance thin layer chromatography (HPTLC), and liquid chromatography linked to tandem mass spectrometry will be thoroughly examined in this study (LC-MS).

Keywords: Pirfenidone, Analytical methods, HPLC, Broad-spectrum

INTRODUCTION

Pirfenidone is an agent used for the treatment of idiopathic pulmonary fibrosis (IPF). Pirfenidone is an orally active small molecule drug that may inhibit collagen synthesis, down regulate production of multiple cytokines and block fibroblast proliferation and stimulation in response to cytokines. Pirfenidone has demonstrated activity in multiple fibrotic conditions, including those of the lung, kidney and liver. It is being investigated by InterMune. Pirfenidone is a novel agent with anti-inflammatory, antioxidant, and antifibrotic properties. It may improve lung function and reduce the number of acute exacerbations in patients with idiopathic pulmonary fibrosis (IPF)[(2)]. In 2014, it was approved for the treatment of the idiopathic pulmonary fibrosis (IPF) by U.S. Food and Drug Administration [(1)].

Pirfenidone was found to be effective for individuals with varying stages of idiopathic pulmonary fibrosis in a recent phase III multi-national clinical study. It has a favourable benefit-risk balance and is well tolerated in general. However, the most common side effects include gastrointestinal issues, photosensitivity responses, and rash[(3)]. Idiopathic pulmonary fibrosis (IPF) is a deadly, progressive fibrotic lung disease with a three-to-five-year survival rate in the absence of proven effective treatment. IPF is caused by persistent epithelial cell damage and the abnormal activation of progressive fibrosis. As a result, as described in recent clinical studies, the

therapy strategy for IPF has switched from corticosteroids and/or immune suppressants to antifibrotic drugs[4].

Chemically pirfenidone is known as 5-methyl-1-phenyl-1,2-dihydropyridin-2-one, the structure of the pirfenidone is shown in (figure 1). Although the precise mechanism of action of pirfenidone and its specific molecular targets have yet to be elucidated[5,6]. The molecule has demonstrated anti-fibrotic, anti-inflammatory, and antioxidant activity. One vital anti-fibrotic mechanism involves suppression of TGF-β1 (transforming growth factor-β1), a key cytokine involved in fibrogenesis and extracellular matrix production[7,8,9].

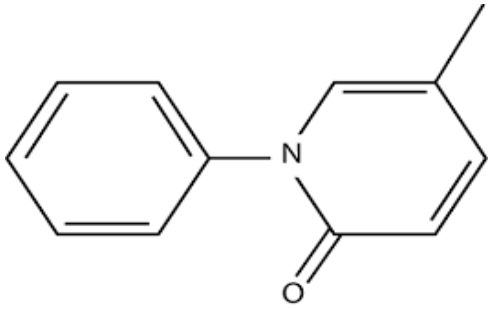

Fig 1: Structure of Pirfenidone

Data Collection

The approach utilised in generating this review article is a literature research, which involves locating sources or literature in the form of primary data in the form of official books and international journals published in the previous 20 years (2000-2020). In addition, pirferidone analysis in pharmaceutical preparations and biological matrices was performed as part of this review article's data search utilising web media with keywords. The key references for this review study were found using a reputable web search engine such as ScienceDirect, NCBI, Researchgate, Google Scholar, and other published and trustworthy publications.

ANALYTICAL METHODS

Spectrophotometry

For the process of method development spectroscopic technique was the most important technique. In our pharmacopoeias this technique is based on the natural absorption of UV radiations, and other chemical reactions. Spectroscopy is totally based on the quantitative measurement, properties transmission, and wavelength function[10]. This method has been great advantage to save time, or expenditure of labor. Several spectrophotometric techniques are used to determine the amounts of Pirferidone in raw materials and pharmaceutical formulations. Table 1 showsthe spectrophotometric published methods.

Table1: Pirferidone analysis using Spectrophotometry technique

Author	Drug name	Matrix	Method or reagent	Wavelength	Linearity range	Ref
P.Ravisankar	Pirfenidone	Bulk and tablet	UV spectrophotometer SL 2203	UV-315nm	2-10 µg/mL	11
S. Naga Gayatri and V. M. Biju	Pirfenidone	Tablet	Water	UV-220nm	50 ppm – 3.125 ppm	12
Khan mohammad mujeeb G et a..,	Pirfenidone	Bulk and Formulation	Methanol	UV-317nm	15-40 µg/mL	13
V. K. Parmar et al..,	Pirfenidone	Formulation	Methanol	UV-317nm	3-25 µg/ml	14
Thorat, S. G. et al..,	Pirfenidone	Tablet	Methanol	UV-311nm	10-60µg/ml	15

Irina M. Le-Deygen, Anastasia S. Safronova et al..,	Pirfenidone and DPPC Liposomes	Interactions Studies	sodium-phosphate-buffered solution	UV-310nm	Upto 45 µg/ml	16
Naga Gayatri Sambhani et al..,	Pirfenidone	Micelle-En hanced Spec trofluorimetric Deter mination of Pirfenidone	Tween - 80 micellar medium	396 nm	0.5 - 5 µg/mL	33

Chromatographic Methods

Chromatograpic techniques are the major techniques which are used for the separation of complex mixture of compounds and their molecules. The chemical compounds, and biological components are very effective to be encountered by this techniques.HPLC methods were widely used chromatographic methods in the analysis of Pirferidone in Formulation[17]. LC-MS/MS, LC-MS and UPLC use for estimation of Pirferidone in Plasma. HPLC method also developed for determination of Pirferidone in pharmaceutical dosage form and plasma. Table 2showsthe HPLC published methods.

Table2: Pirferidone analysis using HPLC technique

Author	Drug name	Matrix	Column	Mobile phase	Wave length	Linearity range	Ref
Ravisankar P., Anusha Rani K et al..,	Pirfenidone	Pharmaceutical dosage form	Welchrom C18 (250 mm × 4.6 mm, 5 µm)	acetonitrile: water 50:50 v/v	315nm	2-10 µg/mL	18
C. Vanitha, Sravani Singirikonda.	Pirfenidone	Bulk and tablet	Symmetry C18 (150 mm x 4.6, 5 micron)	orthophosphoric acid buffer: acetonitrile (65:35).	315nm	13.4-80.1 µg/mL	19
Bodempudi, S. , Babur, R. and Reddy, K.	Pirfenidone	Impurities in Pirfenidone drug	Zorbax RX-C18 column (250 mm x 4.6, 5 micron	0.02 M KH2PO4 buffer and acetonitrile (Gradient)	220nm	-	20
V. K. Parmar et al..,	Pirfenidone	Formulation	C18 Zorbax Eclipse plus	Acetonitrile:Water (35:65 %v/v)	317nm	0.2-5.0 µg/mL	21
More Siddhant et al	Pirfenidone	Bulk and Formulation	C18 analytical column (250 × 4.6 mm, 5 µm) u	Acetonitrile: Methanol: Water (65:15:20)	317nm	5-25 µg/ml	22
Snehal Ganpat Tekawade et aj..,	Pirfenidone	Pharmaceutical dosage form	GRACE C18 analytical column (250×4.6mm , 5µ)	Methanol: Water (90:10 v/v)	224 nm and 314 nm	10-50 µg/ml	23
Dona Sara Kurian, Sara Kurian	Pirfenidone	Bioanalytical method	Phenomenex C-18 RP column (25 cm x 4.6	gradient mode	324nm	50–250ng mL	24

			mm, 5µm ID)				
ZHANG Xiao-ling et al..,	Pirfenidone	Related substances in Pirfenidone drug	Diamonsil C18(250 mm×4.6 mm,5 µm)	acetonitrile-water containing 0.2% acetic acid(33:67)	310nm	34.38-171.91 mg.L^{-1}	25
Rajasekaran, A., and M. Deepthi	Pirfenidone	-	C18 column	0.5% triethylamine (pH adjusted to 4.5 with orthophoshoric acid) Acetonitrile: Methanol (90:10)(55:45)	315nm	10 to 50 µg/ml	26
Emrah Dural, Sema Tulay Koz et al..,	Esomeprazole and pirfenidone	in rat plasma	C18 reverse-phase column (4.6 mm x 250 mm, 5 [micro]m)	Phosphate buffer and acetonitrile (60:40, v/v)	305nm	0.87-8296.87 ng/mL and 0.45-238.60 ng/mL	27

HPTLC

This approach was widely utilised for the identification, estimate, and verification of drug compounds' analytical profiles across the world. It is a cutting-edge technology that will be acknowledged as a significant instrumental technique for drug analysis. Because of its quick separation action and adaptability, it can examine a wide range of medication components in the pharmaceutical industry. The key advantage of this technology is that it can test the drug in a short amount of time and is simple to handle or clean crude drug samples. With the aid of this approach, we may describe the chromatogram for a huge number of parameters in no time[28,29].Table 3showsthe HPTLC published methods.

Table3: Pirferidone analysis using HPLC technique

Author	Drug name	Matrix	Column	Mobile phase	Wave length	Linearity range	Ref
Thorat, S. G. et al..,	Pirfenidone	Tablet	precoated Silica Gel 60 F254 TLC	Toluene: Methanol, 8:2 v/v.	311nm	800-1600 ng/spot	30
Ritesh Bhole et al..,	Pirfenidone	Stability indicating	Precoated silica gels plates	Methanol: ethyl acetate: toluene (1:2:7 v/v)	315nm	-	31
Sonali G. Thorat, Rupesh V. Chikhale	Pirfenidone	In rat plasma	Precoated silica gels plates	toluene–methanol in the ratio of 8:2	315nm	100–1,200 ng/spot	32

Electrophoretic Technique

Capillary electrophoresis is a highly essential technique for drug analysis in pharmaceutical industries, and its proper name is capillary electrophoresis (CE). Capillary electrophoresis is entirely reliant on the electric charge of ions via an electromagnetic field. This method proved beneficial for separating and analysing medication components. During the electrophoresis process, the solute (sample) was passed through a capillary to the detector, and the area of travelling the components of a specific peak is directly proportional to the concentration of compound, and as a result of this phenomenon, quantitative analysis of samples was performed by this useful technique[34]. Table 4 shows the Electrophoretic published methods.

Table 4: Pirferidone analysis using Electrophoresis technique

Author	Drug name	Detection	Stationary phase	Buffer	Voltage	Linearity range	Ref
Salvatore Sotgia et al..,	Pirfenidone	In plasma	80 cm, 75 µm i.d. uncoated fused-silica capillary	35 mmol/L N-lauroylsarcosine sodium salt surfactant added with a 16 mmol/L sodium 1-heptanesulfonate solution	30 kV	6.25–200 µmol/L	35

Hyphenated Techniques

The separation technique based on coupling separation and online separation will be used to construct a novel approach for drug analysis known as hyphenated methodologies. In recent years, this approach has played a significant role in the advancement, development, and use of pharmaceuticalsin pharmaceutical analysis. The medications were determined material from biological sources is the key analysis stage for the invention of new pharmaceuticals and the development of drug products[36]. To improve the potential of drug analysis, hyphenated approaches like as LC-MS, GC-MS, LC-NMR, CE-MS etc.., Table 5 shows Hyphenated techniques Characteristics methods available in literature.

Table 5: Pirferidone analysis using Hyphenated techniques

Author	Drug	Matrix	Stationary phase	Mobile phase	Study	Detection	Method	Ref
Shuhua Tong, Xianqin Wang et al..,	Pirfenidone	In Rat plasma	C18 column	40:60(v/v) Acetonitrile-0.1% formic acid	Pirfenidone in Rat Plasma	Electrospray ionization source	LC-ESi-MS/MS	37
C.-Y. Li et al..,	Pirfenidone	In Human plasma	Agilent ZORBAX SB C18 (3.0 mm × 100 mm, 3.5 µm)	Water (0.5% formic acid) and acetonitrile (50/50)	Pirfenidone & its metabolite in Human Plasma	Electrospray ionization source	LC--MS/MS	38
Yu-Guan Wen et al..,	Pirfenidone	In human plasma	Agilent Zorbax Plus C18 column	Acetonitrile and aqueous ammonium formate solution (5 mM) containing 0.1% formic acid (60 : 40, v/v).	Pirfenidone &its metabolite in Human Plasma	positive ionization mode,	LC-TMS	39
Ming-Luan Chen et al..,	Pirfenidone	In Rat Plasma	On-line trapping column: Acquity BEH C18, 5 x 2.1 mm, 1.7 µm,	Mobile phase containing 10% MeOH.	Pirfenidone and Metabolites in Rat Plasma	Coupling On-Line Fractionation with LC-MS/MS	LC-MS/MS	40

Shuanghu Wang et al..,	Curcumin and Pieferidone	In Rat Plasma	BEH HILIC (2.1 mm × 100 mm, 1.7 μm)	Acetonitrile and 10 mm ammonium formate buffer (containing 0.1% formic acid)	Pirfenidone and Curcumin in Rat Plasma	XevoTQD triple-quadrupole mass spectrometer	UPLC-MS/MS	41

CONCLUSION

In conclusion, a broad range of techniques are available for the analysis of Pirfenidone in biological samples and pharmaceutical formulations. The analysis of the published data revealed that the HPLC methods were extensively used for the determination of Pirfenidone in various matrices like plasma, serum and urine. For determination of Pirfenidone in biological samples, were commend the HPLC–MS/MS method, since this method combines the HPLC separation ability with MS sensitivity and selectivity, allowing the unambiguous identification of Pirfenidone and its metabolites. For analysis of Pirfenidone in pharmaceuticals, HPLC with UV detection is applicable because this method provides accurate results and low cost compared to more advanced detection techniques. This review carried out an overview of the current stateof-art analytical methods for the determination of Pirfenidone.

REFERENCES

1. GuoJingwen, YangZhifeng, JiaQiang, BoCunxiang, ShaoHua, ZhangZhenling. Pirfenidone inhibits epithelial-mesenchymal transition and pulmonary fibrosis in the rat silicosis model. Toxicol Lett.2019;300:59-66. doi: 10.1016/j.toxlet.2018.10.019, PMID 30394303.
2. Available from: https://go.drugbank.com/drugs/DB04951.
3. JiangNan, MaMingyang, LiYunyan, SuTing, ZhouXue-Zhi, YeLei, YuanQing, ZhuPeiwen, MinYoulan, ShiWenqing, XuXiaowei, LvJinlei, ShaoY. The role of pirfenidone in alkali burn rat cornea. Int Immunopharmacol.2018;64:78-85. doi: 10.1016/j.intimp.2018.08.032, PMID 30153530.
4. TaniguchiH, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, Taguchi Y, Takahashi H, Nakata K, Sato A, Takeuchi M, Raghu G, Kudoh S, Nukiwa T, Pirfenidone Clinical Study Group in Japan. Pirfenidone in idiopathic pulmonary fibrosis.Eur Respir J.2010;35(4):821-9. doi: 10.1183/09031936.00005209, PMID 19996196.
5. BallesterBeatriz, MilaraJavier, CortijoJulio.Pirfenidone anti-fibrotic effects are partially mediated by the inhibition of MUC1 bioactivation. Oncotarget. 2020Apr14;11(15):1306-20. doi: 10.18632/oncotarget.27526, PMID 32341751.
6. FDA Approved Drug Products: Esbriet (pirfenidone) for oral use.
7. ChoMonique E, KoppJeffrey B.Pirfenidone: an anti-fibrotic therapy for progressive kidney disease. Expert Opin Investig Drugs. 2010Feb;19(2):275-83. doi: 10.1517/13543780903501539, PMID 20050822.
8. BiernackaAnna, DobaczewskiMarcin, FrangogiannisNikolaos G.TGF-beta signaling in fibrosis. Growth Factors. 2011Oct;29(5):196-202. doi: 10.3109/08977194.2011.595714, PMID 21740331.
9. RuwanpuraSaleela M, ThomasBelinda J, BardinPhilip G.Pirfenidone: molecular mechanisms and potential clinical applications in lung disease. Am J Respir Cell Mol Biol.2020Apr;62(4):413-22. doi: 10.1165/rcmb.2019-0328TR, PMID 31967851.
10. ChauhanA, Mittu B, Chauhan P. Analytical method development and validation: a concise review. J Anal Bioanal Tech.2015;6(1):5.
11. RavisankarP. Development of A validated Uv spectrophotometric method for the Quantitative estimation of pirfenidone in bulk drug and marketed tablet, IJPRD.2014;6(09):(025-31).
12. Naga GayatriS, Biju VM. Assay of pirfenidone by UV spectrophotometry .J Chem PharmRes.2016;8(7):36-41.
13. KhanMohammad, MujeebG, PawaraPritamI, Chaudhari PrashanthJ, Shirkedkar AtulA. Development and validation of zero and first-order derivative area under curve spectrophotometric methods for determination of pirfenidone in bulk material and pharmaceutical Formulation.Asian J Res Chem.2019;12(3):129-35.
14. ParmarVK, Desai SB, Vaja T. RP-HPLC and UV spectrophotometric methods for estimation of pirfenidone in pharmaceutical formulations. Indian J Pharm Sci.2014May–Jun;76(3):225-9. PMID 25035534.

15. ThoratSG, Padmane SP, Tajne MR, Ittadwar AM. Development and Validation of simple, rapid and sensitive UV, HPLC and HPTLC methods for the estimation of pirfenidone in tablet dosage form.J Chil Chem Soc.2016;61(2):2978-81. doi: 10.4067/S0717-97072016000200025.
16. Le-DeygenIrinaM, Safronova Anastasia Set al.Cholesterol significantly affects the interactions between pirfenidone and DPPCliposomes: spectroscopic studies, Biophysica 2022. Vol. 2(1).
17. PuozzoChristian, FilaquierChristian, ZorzaGrégoire. Determination of milnacipran, a serotonin and noradrenaline reuptake inhibitor, in human plasma using liquid chromatography with spectrofluorimetric detection. J Chromatogr B Analyt Technol Biomed Life Sci. 2004;806(2):221-8. doi: 10.1016/j.jchromb.2004.03.063, PMID 15171932.
18. RavisankarP, Anusha Rani K, DevadasuCh, Devala Rao G. A novel validated RP-HPLC method for the determination of pirfenidone in pharmaceutical dosage forms.PharmLett.2014;6(5):19-29.
19. VanithaC, SingirikondaSravani. Development of a Validated Stability Indicating Rp-Hplc Method for the Estimation of pirfenidone in Bulk Drug and Tablet Dosage form.J PharmResInt.2021;33(29B):110-8. doi: 10.9734/jpri/2021/v33i29B31595.
20. Bodempudi Suresh Babu, Babur Ravichandra, Srinivasa Reddy Konda. Development and substantiation of a RP-HPLCmethod for monitoring of impurities in pirfenidone drug substance. Am J AnalChem.2015;6(13):1019-29.
21. ParmarVK, Desai SB, Vaja T. RP-HPLC and UV spectrophotometric methods for estimation of pirfenidone in pharmaceutical formulations. Indian J Pharm Sci.2014May–Jun;76(3):225-9. PMID 25035534.
22. More Siddhant, Dalwate Shweta, Chandramore Nehal, JadhavVaishali, JainAshish. Development ofchromatographicmethodandvalidationforestimationofpirfenidoneinbulkandpharmaceuticaldosageform. Int ResJ Pharm.2019;10(7):45-50.
23. TekawadeSnehalGanpat, Dr.Pingle Ashok Pandurang, Sonawane Rina Mohan, Sonare Rutuja Prabhakar. Chromatographic methoddevelopmentandvalidationforestimationofpirfenidoneinpharmaceuticaldosageform, EJBPS.2018;5(8):552-8.
24. KurianDonaSara, KurianSara. Bioanalytical method development and validation of pirfenidone by Rp-Hplc method and its application to the determination of drug food interaction study in Wisterrats [masters thesis].
25. ZHANGXiao-linget al.Determination of pirfenidone and its related substances by RP-HPLC. Anhui Medical and Pharmaceutical Journal. 2009.
26. RajasekaranA, Deepthi M. Analytical Method Development and Validation of isocratic RP-HPLC separation of pirfenidone and Robustness testing by Chemometric Analysis. Inventi Impact Pharm Anal QualAssur.2014.
27. DuralEmrah, Sema Tulay Kozet al.Development and validation an HPLC - UV method for determination of esomeprazole and pirfenidone simultaneously in rat plasma: application to a drug monitoring study.J Fac Pharm IstanbUniv.2021;51(1).
28. SinghRKR, Rathnam MV, Singh SJ, VegesnaRVK. Determination of camylofin dihydrochloride and nimesulide in Pharmaceutical preparation by Gas chromatography. AmJ AnalChem. 2011;02(8):944-52. doi: 10.4236/ajac.2011.28110.
29. NatesanS, Thanasekaran D, Krishnaswami V, Ponnusamy C. Improved RP-HPLC method for the simultaneous estimation of tranexamic acid and mefenamic acid in tablet dosage form. PharmAnal Acta. 2011;02(1):115. doi: 10.4172/2153-2435.1000115.
30. ThoratSG, Padmane SP, Tajne MR, Ittadwar AM. Development and Validation of simple, rapid and sensitive UV, HPLC and HPTLC methods for the estimation of pirfenidone in tablet dosage form.J Chil Chem Soc.2016;61(2):2978-81. doi: 10.4067/S0717-97072016000200025.
31. BholeRitesh, JagtapSR, BondeCG, ZambareYB. Development and validation of stability indicating HPTLC method for estimation of pirfenidone and characterization of degradation product by using mass spectroscopy, Buketov Karaganda State University in.Bull Karaganda Univ.2020;99.
32. Thorat, Rupesh V. Chikhale. Determination and pharmacokinetic study of pirfenidone in ratserum by high-performancethin-layer chromatography.J ChromatogrSci.2016;54(7):1115-9. doi: 10.1093/chromsci/bmw067, PMID 27406123.
33. SambhaniNagaGayatri, BijuValsala Madhavan Nair. A micelle-enhanced spectrofluorimetric determination of pirfenidone: application to content uniformitytesting and humanurine.J Fluoresc.2018;28(4):951-7. doi: 10.1007/s10895-018-2258-8, PMID 29974315.
34. GeorgiouCA, Valsami GN, Macheras PE, Koupparis MA. Automated flow-injection technique for use in dissolution studies of sustained-release formulations: application to iron (II). J Pharm BiomedAnal. 1994;12(5):635-41. doi: 10.1016/0731-7085(93)e0015-f, PMID 7948184.
35. SotgiaSalvatore, FoisAG, SotgiuE, ZinelluA, PaliogiannisP, MangoniAA, CarruC.Micellar electrokinetic capillary chromatographic determination of pirfenidone and 5-carboxy-pirfenidone by direct injection of plasma from patients receiving treatment for idiopathic pulmonary fibrosis (IPF).MicrochemJ.2020;154. doi: 10.1016/j.microc.2019.104536.

36. GulW. Metformin: methods of analysis and its role in lowering the risk of cancer. J Bioequiv Availab. 2016;08(6):254-9. doi: 10.4172/jbb.1000305.
37. TongShuhua, WangXianqin, JiangH, XuX, PanY, ChenK, WuJ, XuQ, DengJ, HuG. Determination of pirfenidone in ratplasma by LC–MS-MS and its application to a pharmacokineticstudy.Chromatographia.2010;71(7-8):709-13. doi: 10.1365/s10337-010-1538-5.
38. LiC-Yet al. Determination of pirfenidone and its major metabolite in human plasma by LC-MS/MS analysis.ChinPharmacolBull;33(5):696-703.
39. WenYu-Guan, LiuXia, HeXiu-Ling, ShangDe-Wei, NiXiao-Jia, ZhangMing, WangZhan-Zhang, HuJin-Qing, QiuChang. Simultaneous determination of pirfenidone and its metabolite in human plasma by liquid chromatography-tandem mass spectrometry: application to a pharmacokinetic study.J Anal Toxicol.2014;38(9):645-52. doi: 10.1093/jat/bku104, PMID 25248491.
40. ChenMing-Luanet al. Determination of pirfenidone and metabolites in ratplasma by couplingon-linefractionation with LC-MS/MS, Altasciences.
41. WangShuanghu, LinZ, SuK, ZhangJ, ZhangL, GaoZ, WangZ, MaJ, WangX.Effect of curcumin and pirfenidone on toxicokinetics of paraquat in rat by UPLC–MS/MS.Acta Chromatographica.2018;30(1):26-30. doi: 10.1556/1326.2017.00175.