Determination of Captopril in Rat Plasma by LC-MS/MS in Presence of Apigenin

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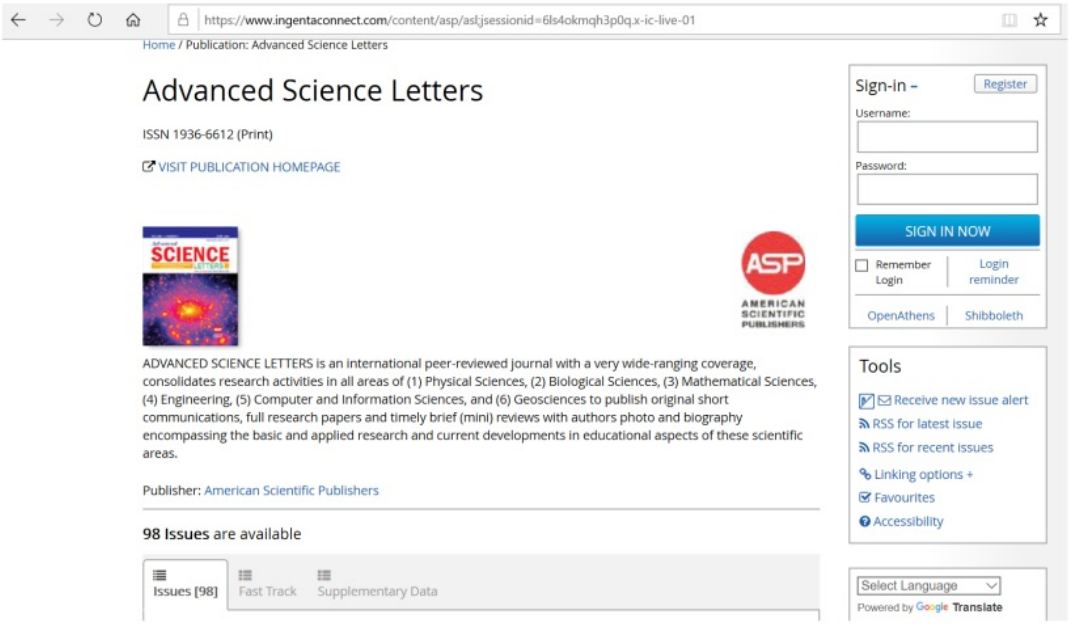
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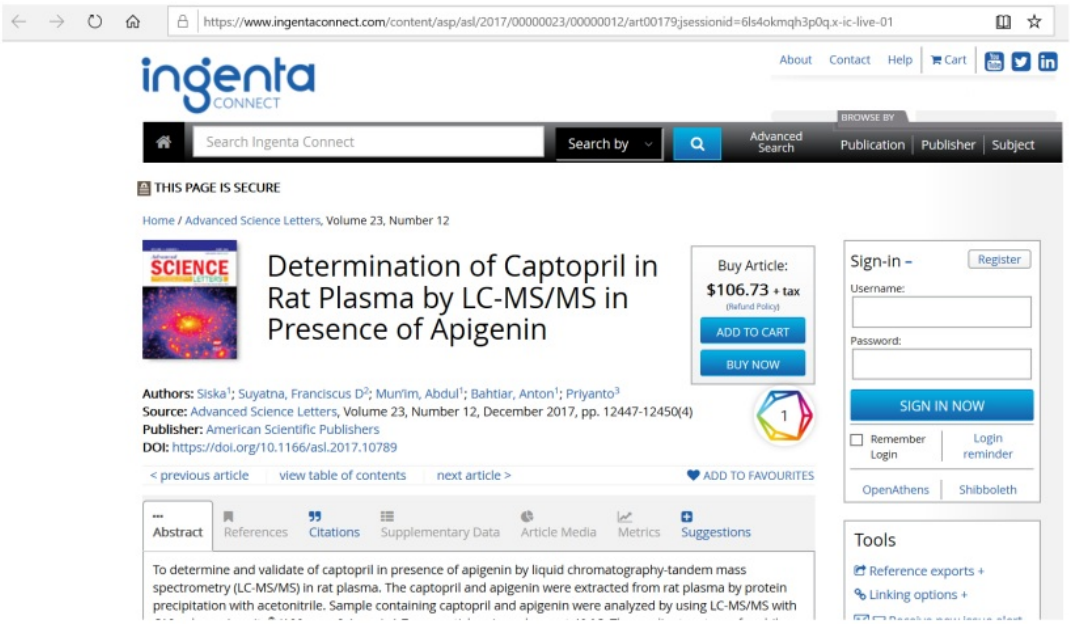
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To determine and validate of captopril in presence of apigenin by liquid chromatography-tandem mass spectrometry (LC-MS/MS) in rat plasma. The captopril and apigenin were extracted from rat plasma by protein precipitation with acetonitrile. Sample containing captopril and apigenin were analyzed by using LC-MS/MS with
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Determination of Captopril in Rat Plasma by LC-MS/MS in Presence of Apigenin

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To determine and validate of captopril in presence of apigenin by liquid chromatography-tandem mass spectrometry (LC-MS/MS) in rat plasma. The captopril and apigenin were extracted from rat plasma by protein precipitation with acetonitrile. Sample containing captopril and apigenin were analyzed by using LC-MS/MS with C18 column Acquity® (100 mm × 2.1 mm), 1.7 μm particles size column at 40 °C. The gradient system of mobile phase composition was a mixture of 0.1% formic acid and acetonitrile (60; 40 v/v), with flow rate 0.3 ml/second. Mass detection was performed on Waters Xevo Triple Quadrupole equipped with an electrospray ionization (ESI) source in positive ion mode in the multiple reaction monitoring (MRM) modes. Captopril was detected at m/z 415 > 216.16, apigenin was detected at m/z 271.13 > 153.07 and propranolol an internal standard was detected at m/z 260 > 183.17. Results: The method was validated according to EMEA guidelines which showed good reproducibility and linearity of 0.9992, the LLOQ were 10 ng/ml for captopril. The precision (%CV) value of Within-run and between-run analysis is 3.90–10.90% and 3.77–8.13% whereas the accuracy (bias) of captopril was less than 20%. Stability studies revealed that captopril has been stable for 6 hours at room temperature, three freeze-thaw cycles, and at least 120 days at −40 °C. Conclusion: The developed LC-MS/MS method is valid to evaluate captopril in present of apigenin *in vitro* and meet the requirement of linearity, accuracy, selectivity, precision, matrix effect, and stability according to EMEA 2011.

Keywords: Validated Method, LC-MS/MS, Captopril, Apigenin, Apium Graveolens.

1. INTRODUCTION

Captopril is the first drug from the class of Angiotensin Converting Enzyme inhibitors (ACEI) which works by preventing the changes of angiotensin I to angiotensin II (potential vasoconstrictor and aldosterone secretion stimulus). ACE inhibitors prevent the degradation of bradykinin and stimulate the synthesis of compounds other vasodilators include prostaglandin E2 and prostacyclin, causing vasodilation and decreased secretion of aldosterone causes sodium and water excretion, and potassium retention. As a result, a decline in blood pressure in patients with hypertension.[1] Apigenin was one of the bioactive marker compounds from *Apium graveolens* (celery), that is used in traditional medicine for a diuretic, antihypertensive.[2,3] Herbs are sold as food supplements, because of that, the companies are not required to prove the efficacy of the herbs or determine the side effects or interaction of the products.[4] Although most people believe that herbs are harmless plants, there are some drugs were developed from plants, such as digitalis, morphine, atropine, and several chemotherapeutic agents. Herbs can effect body functions; therefore, when herbs are taken together with drugs, interaction are possible. Herbal medicine has increased in popularity, but they do not inform their medical practitioners of such use.[5] Herbs preparation in combination with a synthetic drug taken simultaneously may interact with the synergistic effect result or can increase the side effect.[6] Because of that, it is necessary to study the interaction between drug and herb. To support clinical investigations, especially in pharmacokinetics interaction, a reliable analytical method with adequate sensitivity is necessary. Several HPLC, LC-UV and LC-MS/MS method have been conducted previously for the determination of captopril in biological sample.[7] However, to the authors' knowledge, the combination of captopril and apigenin has not been reported. The present study describes a simple, rapid, precise, and accurate LC-MS/MS method for determining captopril in present of apigenin in rat plasma.

2. EXPERIMENTAL DETAILS

2.1. Material and Methods

Captopril and propranolol were obtained from Zhejiang Huahai Pharmaceutical and apigenin from Shaanxi Jintai Biological Engineering. Acetonitrile, 2,4-dibromoacetophenon, and

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methanol were HPLC grade and were purchased from Merck. The reagents that used were of analytical or reagent grade purity. Ultrapure water was generated by Millipore Direct-Q® ultra-pure water system. Sprague-Dawley rat plasma was supplied by Bogor Agriculture Institute and used as a blank matrix in the preparation of calibration standards and QC samples.

2.2. Standard Solutions, Calibration Standards, and QC Sample Preparation

Primary stock solutions of captopril, respectively, with the concentration of 200 μg/ml was prepared by dissolving 40 mg in 100 ml water. Primary stock solutions of propranolol (1 mg/ml) and apigenin (1 mg/ml) were prepared by dissolving 40 mg in 100 ml methanol. Calibration standards and QC samples were prepared by diluting the stock solution with Sprague-Dawley rat plasma to form the calibration standards of captopril in the present of apigenin (10, 25, 50, 100, 250, and 500 ng/ml) and QC samples (30, 200, and 400 ng/ml). A stock solution of 2,4-dibromoacetophenon with concentration 520 μg/ml was prepared by dissolving 52 mg in 100 ml methanol.

2.3. Preparation of Sample

To clean up the plasma samples, a simple protein precipitation procedure was applied.[8] 180 μl of plasma containing certain concentrations of captopril and apigenin were added 20 μl 2,4-dibromoacetophenon working solution and ammonia 5%, vortex-mixed for 30 Sec and stored at 25 °C for 30 Min, after that added 20 μl formic acid 15%, propranolol (1 μg/ml) and 600 μl acetonitrile, vortex-mixed for 30 Sec and centrifuge at 12000 rpm for 5 Min, after that the supernatant was transferred to an autosampler vial and 5 μl were injected into the LC-MS/MS system.

2.4. Chromatographic Conditions

The chromatography was performed on C18 column Acquity® (100 mm × 2.1 mm), 1.7 μm particles size column at a temperature of 40 °C. The gradient system of mobile phase composition was a mixture of 0.1% formic acid and acetonitrile (60; 40 v/v), with flow rate 0.3 ml/second. Mass detection was used Waters Xevo Triple Quadrupole equipped with an electrospray ionization (ESI) source in positive ion mode in the multiple reaction monitoring (MRM) modes.

2.5. Validation Method

The validation of LC-MS/MS method by examining its precision, accuracy, sensitivity, selectivity, matrix effect and stability profiles of captopril in presence of apigenin accordingly with EMEA 2011.

Animals used in this study were approved by the Health Research Ethics Committee of the Faculty of Medicine, University of Indonesia. The reference number for notice of approval was 666/UN2.F1/ETHICS/2016.

3. RESULTS AND DISCUSSION

3.1. Optimization of LC-MS/MS Parameters

To quantify captopril in presence of apigenin in rat plasma sample, needed a selective and sensitive methodology for accurate pharmacokinetic examination especially at low plasma level. Captopril is very unstable, undergoes to oxidation, the degradation product being the dimer and also binds to endogenous compounds (cysteine, glutathione). To improve stabilize the compound a derivatizing agent 2,4-dibromoacetophenon can be used, which prevents captopril binding to plasma constituents and is also a chemical stabilizer.[7]

Mass detection was used Water Xevo TQD equipped with electrospray ionization (ESI) source in positive ion mode in the multiple reaction monitoring (MRM) modes. The following operational parameter of the ions cone and collision energies are presented in Table I. Captopril was detected at m/z 415 > 216.16, apigenin was detected at m/z 271.13 > 153.07 and propranolol as an internal standard was detected at m/z 260 > 183.17.

The full spectrum scan was dominated by protonated molecules m/z 415 for captopril and 271,13 for apigenin, and the major fragmentations observed in each product spectrum were at m/z 216,16 and 153,07 (Figs. 1 and 2). Chromatogram of captopril, apigenin, and propranolol simultaneously is given in Figure 3.

3.2. Validation Assay

A validity test of LC-MS/MS method includes its selectivity, sensitivity, precision, accuracy, matrix effect and stability[9] profiles of captopril in the presence of apigenin.

3.3. Calibration Curve and Lower Limit of Quantification (LLOQ)

The calibration curves were linear over the concentration range of 10–500 ng/ml and linearity of 0.9992, the LLOQ were 10 ng/ml. The precision value (%CV) of Within-run and between-run analysis is 3.90–10.90% and 3.77–8.13% was less than 20% (Table II).

3.4. Selectivity

The selectivity was evaluated by analyzing blank plasma sample and blank plasma spiked with captopril, apigenin, and propranolol (internal standard). The result showed that there was no interference endogenous compound from the blank plasma of the six different sources, whereas the %diff of captopril was less than 20%.

3.5. Carry Over

Carry over value after high concentration injection was 2.26% for captopril and 1.22% propranolol from LLOQ response, with the presence of apigenin. The value of carrying over-fulfilled the acceptance criteria for analyte <20% and for the internal standard <5%.

3.6. Precision and Accuracy

Precision and accuracy of captopril in presence of apigenin were calculated by within run and between run variation of QC sample

Table I. Result of optimization detection of LC-MS/MS.

Compound	Parent (m/z)	Daughter (m/z)	Cone voltage	Collison energy	Area
Captopril	415	216,16	35	17	$3{,}05 \times 10^5$
Propranolol	260	183,17	42	17	$5{,}59 \times 10^6$
Apigenin	271,13	153,07	61	31	$7{,}03 \times 10^6$

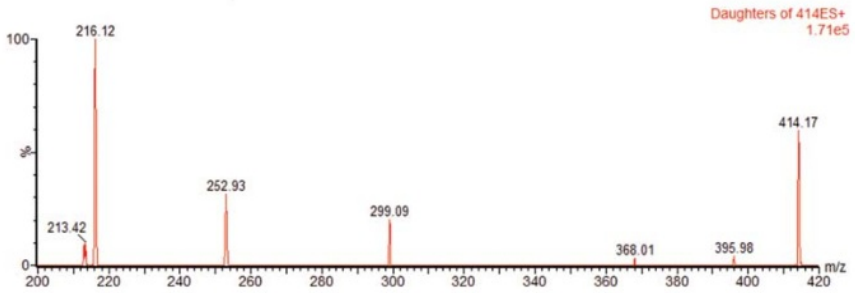

Fig. 1. Fragmentation of ion mass spectrum of captopril.

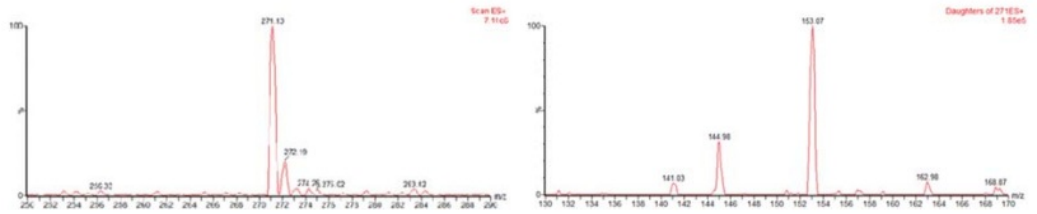

Fig. 2. Fragmentation of ion mass spectrum of apigenin.

in five replication at four concentration as shown in Table II. The precision (%CV) value of within run and between run analysis is 3.90–10.90% and 3.77–8.13%, whereas the accuracy (%diff) of captopril less than 20%. The within run and between run precision and accuracy values indicate the adequate reliability and reproducibility of the method within the analytical range.

3.7. Matrix Effect

Ion increasing effects due to matrix constituents were observed which the value of matrix effect on the low concentration 30 ng/ml was 2,31–2,35% (%CV), was less than 15%.

3.8. Stability Test

The stability profiles of captopril in the presence of apigenin were assessed with different temperature and storage condition and was performed at QCL and QCH in three replicates. The standard solution stability was evaluated after storage at 25 °C for 28 days. Such investigations included short-term stability study (6 h at 25 °C), long term stability study (−40 °C for 120 days), stability after three freeze-thaw cycles (< −20 °C to 25 °C) and

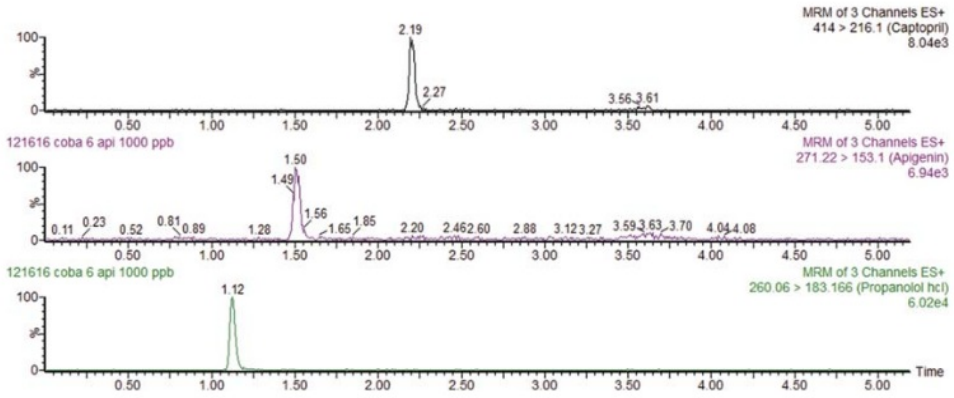

Fig. 3. Chromatogram of captopril, apigenin, and propranolol. The chromatography was performed on C18 column Acquity® (100 mm × 2.1 mm), 1.7 μm particles size column at a temperature of 40 °C. The gradient system of mobile phase composition was a mixture of 0.1% formic acid and acetonitrile (60; 40 v/v), with flow rate 0.3 ml/second, run time 5 Min.

Table II. Accuracy and precision of captopril in presence of apigenin.

	Konsentrasi (ng/ml)	Mean measured concentration (ng/ml) ± SD ($n = 5$)	(%CV)	(%diff)
Within-run	LLOQ (10)	9.73 ±0,38	3.90	−6.50–3.58
	QCL (30)	29.68 ±3,24	10.90	−14.06–11.27
	QCM (200)	199.81 ±12,20	6.10	−8.90–8.22
	QCH (400)	399.61 ±29,56	7.40	−12.81–3.11
Between-run	LLOQ (10)	10.21 ±0.83	8.13	−13.82–12.21
	QCL (30)	31.38 ±1.68	5.35	−5.32–14.41
	QCM (200)	212.76 ±8.02	3.77	−0.66–13.08
	QCH (400)	395.46 ± −1.22	4.21	−7.94–6.07

Table III. Stability of captopril in the presence of apigenin.

Standard solution (25 °C for 28 days) ($n = 3$) −11.74–14.65 (%diff)		
Plasma samples ($n = 3$)	30 ng/ml (±SD)	400 ng/ml (±SD)
After three freezes and thaw cycle (< −20 °C to 25 °C)	32.72 ± 0.43	411.41 ±19.84
Short term stability (6 h at 25 °C)	30.32 ± 0.18	403.86 ±12.17
Post preparative stability (6 h at 25 °C)	32.03 ± 1.10	419.61 ±4.82
Long term stability (−40 °C for 120 days)	30.85 ± 0.25	385.13 ±8.61

post-preparative stability study (6 h at 25 °C). The results of the stabilities study did not deviate by more than 15% compared with freshly prepared samples (Table III).

4. CONCLUSIONS

The LC-MS/MS method has been developed for the determination of captopril in rat plasma in presence of apigenin *in vitro* and showed good selectivity, linearity, accuracy, and precision, matrix effect and stability.

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