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Original Article

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Evaluation of food effects on the pharmacokinetics of *Pelargonium sidoides* and *Coptis* with each bioactive compound berberine and epicatechin after a single oral dose of an expectorant and antitussive agent UI026 in healthy subjects

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ABSTRACT

UI026 is an expectorant and antitussive agent which is a new combination of *Pelargonium sidoides* extract and *Coptis* extract. The bioactive compounds of *Pelargonium sidoides* and *Coptis* extracts were identified as epicatechin and berberine, respectively. This study evaluated the effect of food on the pharmacokinetics (PKs) and safety of UI026. A randomized, open-label, single-dose, 2-treatment, parallel study in 12 healthy male subjects was performed. Subjects received a single oral dose of UI026 (27 mL of syrup) under a fed or fasted condition according to their randomly assigned treatment. Blood samples for the PK analysis were obtained up to 24 hours post-dose for berberine and 12 hours post-dose for epicatechin. The PK parameters were calculated by non-compartmental analysis. In the fed condition, the mean maximum plasma concentration (C_{max}) and mean area under the plasma concentration-time curve from time zero to the last observed time point (AUC_{last}) for berberine were approximately 33% and 67% lower, respectively, compared with the fasted condition, both showing statistically significant difference. For epicatechin, the mean C_{max} and mean AUC_{last} were about 29% and 45% lower, respectively, compared to the fasting condition, neither of which showed a statistically significant difference. There were no drug-related adverse events. This finding suggests that food affects the systemic exposure and bioavailability of berberine and epicatechin.

Trial Registration: Clinical Research Information Service Identifier: KCT0003451

Keywords: Pharmacokinetics; Bioavailability; Berberine; Epicatechin; Herbal Medicine

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INTRODUCTION

Acute and chronic bronchitis is usually caused by a viral or bacterial infection, and symptoms include cough and sputum. Discomfort from cough and sputum can affect the patient's quality of life by causing fatigue and limiting social activities [1]. Therefore, symptomatic treatment that alleviates cough and sputum is as important as the fundamental treatment [2,3]. Expectorant and antitussive agents have been mainly used for symptomatic relief of respiratory diseases [3]. Among them, the combination of herbal extracts such as *Hedera helix*, *Pelargonium sidoides*, and *Coptis chinensis* has proven to relieve cough and sputum and is known to have antibacterial and antiviral activities [4-6]. These herbal extracts are commercially marketed as a fixed-dose combination or single drug formulation for symptom relief and treatment of acute or chronic bronchitis.

UI026 (Lomin Comp Syrup, Korea United Pharm., Inc., Seoul, Korea) is a new composition of a fixed-dose combination of *Pelargonium sidoides* extract and *Coptis* dried extract. Previously, *Pelargonium sidoides* extract, which has antitussive and expectorant properties with antiviral and antibacterial action, is marketed as a single drug formulation (Kalomin Syrup, Korea United Pharm.) for treatment of acute bronchitis. As a symptomatic relief agent for acute and chronic bronchitis, *Coptis* dried extract is marketed in combination with *hedera* leaf dried extract (Synatura Syrup, Anguk Pharmaceutical Co., Ltd., Seoul, Korea). Therefore, the development purpose of UI026 is to obtain a synergic effect in terms of symptom improvement and treatment of acute bronchitis through the combination of *Pelargonium sidoides* extract and *Coptis* dried extract. The bioactive compounds of *Pelargonium sidoides* and *Coptis* dried extract are epicatechin and berberine, respectively [7,8]. Both berberine and epicatechin can inhibit mucin production in sputum and have been shown to induce a bronchodilator activity which has a relaxant effect on the tracheal muscle. Additionally, epicatechin is well known to have potent antiviral and antibacterial activities [9-16].

Food consumption can alter drug bioavailability through effects on absorption. Food intake can change absorption by delaying gastric emptying and increasing gastrointestinal pH [17,18]. The present study was performed to evaluate the effect of food on the pharmacokinetics (PKs) and safety of UI026 (27 mL of syrup). The reason to evaluate the effect of food on the PKs of UI026 is that if it is possible to take it regardless of meals, it can clinically improve the convenience of administration and medication compliance.

METHODS

Study population and study design

This clinical study (Clinical Research Information Service registration number: KCT0003451) was approved by the institutional review board (IRB) of Chungnam National University Hospital (IRB number: CNUH 2017-06-068). Written informed consent was obtained from all subjects prior to the procedure in the study. Moreover, this study was performed in accordance with the ethical principles of the Declaration of Helsinki and the rules of Korean Good Clinical Practices. Healthy adult male subjects were enrolled who were 19–45 years of age with a body weight over 55 kg, and within ± 20% of their ideal body weight. Their eligibility was assessed by medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory test. Subjects had to present no clinically significant abnormalities of the following medical histories: hypersensitivity to any drugs

including the ingredient of the study drug and a history of hepatic, renal, neurological, respiratory, hematological, urinary, psychiatric, cardiovascular, or endocrine disease.

This study was a randomized, open-label, single-dose, 2-treatment, parallel study design. A total of 12 subjects were randomized, of which 6 subjects per group received a single oral dose of UI026 (27 mL of syrup) in the fed or fasted condition according to their randomly assigned treatment. The fasted condition meant that at least 10 hours of fasting was maintained before the administration of the study drug. And in the fed condition, subjects consumed a high-fat meal containing 900 kcal with 35% fat content within 20 minutes prior to the study drug administration. For the PK analysis of berberine, blood samples were obtained at 0 (pre-dose), 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose. For the PK analysis of epicatechin, blood samples were obtained at 0 (pre-dose), 0.33, 0.67, 1, 1.33, 1.67, 2, 3, 4, 6, 8 and 12 hours post-dose.

Bioanalytical method

The collected samples were centrifuged at 3,000 rpm and 4°C for 10 minutes, and the obtained plasma samples were frozen at below −70°C until analysis. The plasma concentration was determined by a liquid chromatography (Berberine, Agilent 1290 series, Agilent Technologies, Santa Clara, CA, USA; Epictechin, Waters Acquity UPLC I-class, Waters Corporation, Milford, MA, USA) coupled with a mass spectrometer (Berberine, TQ5500 system, ABSCIEX, Framingham, MA, USA; Epicatechin, Xevo TQ-s triple quadrupole mass spectrometer, Waters Corporation). The blood samples of berberine and epicatechin were treated with methanol for precipitation of proteins. In addition, berberine-d6 and scopoletin was used as an internal standard for quantitation of berberine and epicatechin, respectively. Chromatographic separation was performed under gradient conditions using a Kinetex 1.7 μ C18 100A (2.0 × 50 mm, 1.7 μm, Phenomenex, Torrance, CA, USA) for berberine and using a ACQUITY UPLC BEH C18 (2.1 × 50 mm, 1.7 μm, Waters Technologies, Drinagh North, Ireland) fore epicatechin. The calibration curves were linear over the range of 1–50 pg/mL for berberine and 0.5–20 ng/mL for epicatechin ($r^2 \geq 0.9969$ and $r^2 \geq 0.9964$, respectively). The in-study imprecision of berberine and epicatechin for the quality control samples was less than 15%, and the accuracy range for both was within 85–115%.

PK analysis

The PK parameters of berberine and epicatechin were estimated by non-compartmental analysis using the WinNonlin® software version 8.2 (Pharsight, Mountain View, CA, USA). The PK evaluation variables were the maximum plasma concentration (C_{max}), area under the plasma concentration-time curve (AUC) from time zero to the last observed time point (AUC_{last}), AUC from zero to infinity (AUC_{inf}), the time to reach the maximum plasma concentration (T_{max}), the half-life ($t_{1/2}$) and apparent total clearance (CL/F) of berberine and epicatechin. The PK parameters were calculated based on the actual sampling time points. The C_{max} and T_{max} were obtained directly from the observed values. The AUC_{last} was calculated using the linear-up/linear-down trapezoidal methods for the absorption and elimination phases, respectively. The AUC_{inf} was calculated as follows: $AUC_{last} + C_{last}/\lambda_z$ (1), where λ_z is the terminal elimination rate constant estimated from a linear regression of the log-transformed plasma concentration versus time. The $t_{1/2}$ was calculated as $\ln(2)/\lambda_z$. The CL/F was calculated as a dose of berberine or epicatechin/AUC_{inf}. If the plasma concentration was below LLOQ, this concentration was regarded as zero before T_{max} and as missing data after T_{max}.

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Statistical analysis

The statistical analysis was performed using SAS® software version 9.4 (SAS Corporation, Cary, NC, USA). Descriptive statistics were used to obtain demographic characteristic, safety and tolerability data, and the PK parameters. All PK parameters are shown as the mean ± standard deviation except for T_{max}, which is presented as the median and range. To evaluate the food effect on the PK of berberine and epicatechin, Mann-Whitney U tests were used and *p*-values lower than 0.05 were considered to indicate statistical significant difference between the 2 conditions.

Safety and tolerability assessment

Safety and tolerability were evaluated by assessing the clinical laboratory tests, 12-lead ECG, physical examination, vital signs and adverse events (AEs). Subjects were required to announce to the investigator if there were any AEs that occurred throughout the entire study period. All AEs that occurred in the subjects were noted during the study, and the investigators determined the relationship between the AEs and the study drug.

RESULTS

Demography

Twelve subjects enrolled and completed the study. Nobody withdrew their consent, and no one dropped out because of AEs. The 12 subjects each were included in the safety analysis and PK analysis. The enrolled subjects were 24.5 ± 4.8 years of age and 174.2 ± 5.3 cm in height and weighed 69.9 ± 7.1 kg (**Table 1**).

PKs results

The mean plasma concentration-time profiles and PK characteristics for the related systemic exposure of berberine and epicatechin were not similar between the fed and fasted conditions. (**Figures 1** and **2**). Under the fed condition, the C_{max} and AUC_{last} for berberine were approximately 33% and 67% lower, respectively, compared with the fasted condition, both showing statistically significant difference. The corresponding values of epicatechin were about 29% and 45% lower, respectively, in the fed condition compared to the fasting condition, neither of which showed a statistically significant difference. The median T_{max} for berberine and epicatechin each were comparable between the fasted and fed conditions (**Table 2**).

Safety results

A total of 2 AEs only occurred in 2 subjects in the fasted condition, and no AE occurred in the fed condition. The AEs that occurred in the fasted condition were diarrhea and nasopharyngitis, and a causal relationship between the study drug and these AEs was considered unlikely or not related. All AEs were mild in intensity and resolved spontaneously. Moreover, no clinically significant changes were observed in the clinical laboratory tests, vital signs, physical examination and ECG throughout the entire study period.

Table 1. Demographic characteristics of the subjects according to the treatments

Parameters	Treatment A (n = 6)	Treatment B (n = 6)	Total (n = 12)
Age (yr)	25.5 ± 6.8	23.5 ± 1.4	24.5 ± 4.8
Height (cm)	176.0 ± 6.5	172.4 ± 3.5	174.2 ± 5.3
Weight (kg)	68.3 ± 6.6	71.5 ± 7.9	69.9 ± 7.1

Data presented as the mean ± standard deviation. Treatment A is the administration of a single oral dose of UI026 (27 mL of syrup) under the fasted condition. Treatment B is the administration of a single oral dose of UI026 (27 mL of syrup) under the fed condition.

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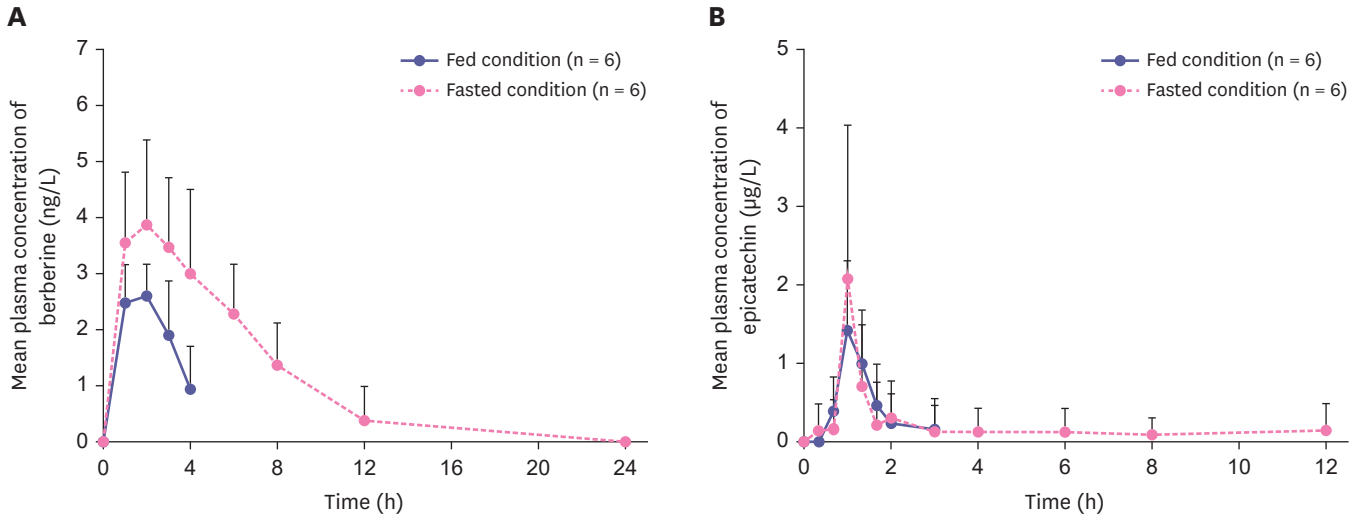

Figure 1. Mean plasma berberine and epicatechin concentration-time profiles after a single oral dose of UI026 (27 mL of syrup) under the fed or fasted condition. Error bars represent the standard deviation; (A) berberine and (B) epicatechin.

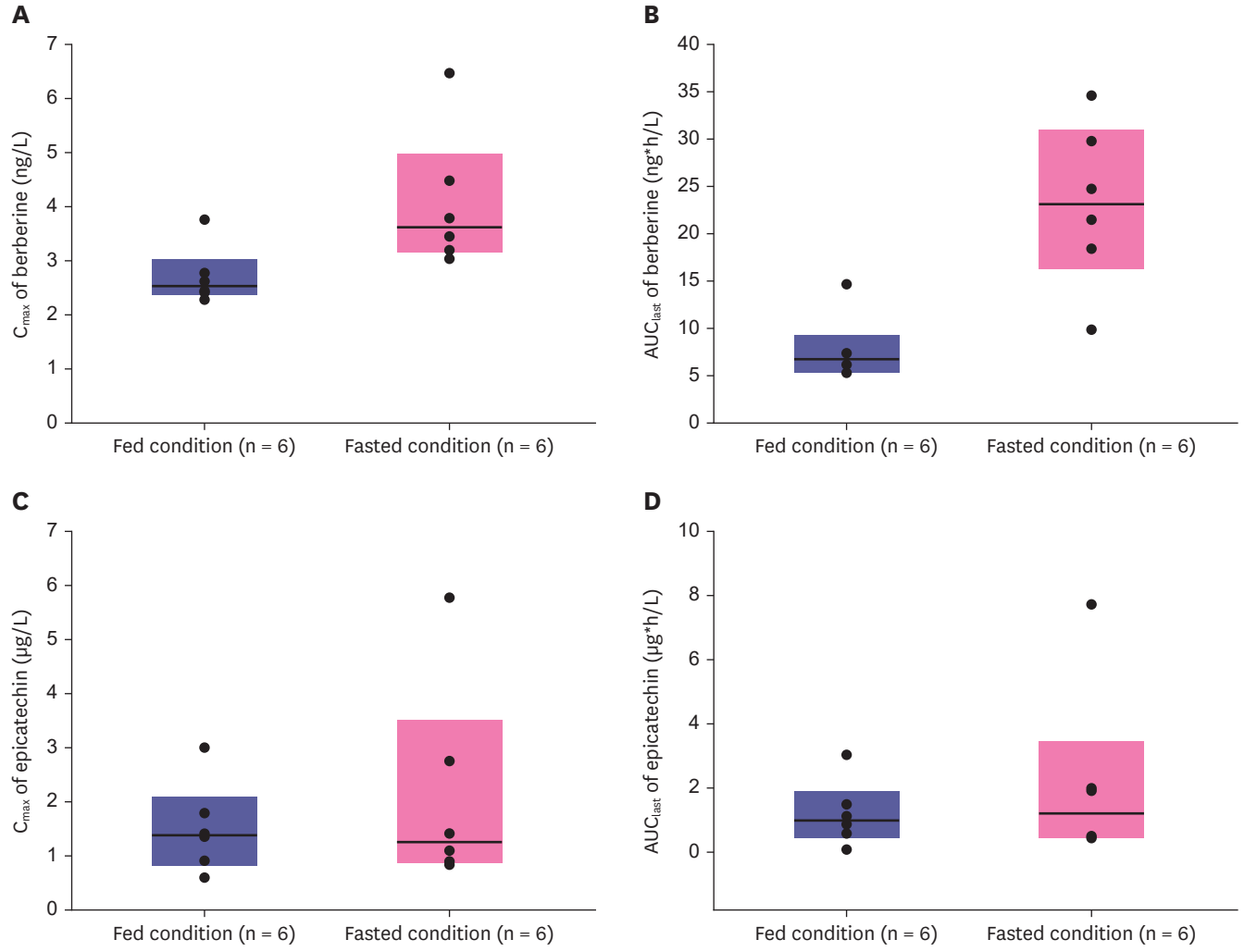

Figure 2. Comparison of (A) C_{max} and (B) AUC_{last} of berberine and of (C) C_{max} and (D) AUC_{last} of epicatechin after a single oral dose of UI026 (27 mL of syrup) under the fed or fasted condition. Horizontal lines and boxes represent the median and interquartile range, respectively. Closed circles (•) indicate the observed value. C_{max}, maximum plasma concentration; AUC_{last}, area under the curve from the time of zero to the last observed time point.

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Table 2. Effect of food on the pharmacokinetic parameters of berberine and epicatechin after a single oral dose of UI026 (27 mL of syrup) in the fed or fasted condition

Pharmacokinetic parameter	Fed condition (n = 6)*	Fasted condition (n = 6)*	*p*-value†
Berberine			
T_{max} (h)	2.00 (1.00–3.00)	2.00 (1.00–2.00)	-
C_{max} (ng/L)	2.71 ± 0.54	4.07 ± 1.28	0.0202
AUC_{last} (h*ng/L)	7.70 ± 3.54	23.17 ± 8.70	0.0082
AUC_{inf} (h*ng/L)	21.66 (-)	32.22 ± 8.64	0.4533
$t_{1/2}$ (h)	5.77 (-)	5.00 ± 2.17	0.4533
CL/F (L/h)	1,458.47 (-)	1,069.72 ± 412.52	0.4533
Epicatechin			
T_{max} (h)	1.00 (1.00–1.33)	1.00 (1.00–2.00)	-
C_{max} (μg/L)	1.51 ± 0.84	2.13 ± 1.92	0.9362
AUC_{last} (h*μg/L)	1.20 ± 1.02	2.17 ± 2.82	0.9362
AUC_{inf} (h*μg/L)	5.91 (-)	19.09 (-)	-
$t_{1/2}$ (h)	2.10 (-)	9.33 (-)	-
CL/F (L/h)	498.25 (-)	176.90 (-)	-

Data is presented as the mean ± standard deviation and coefficient of variation, except for T_{max}, which is presented as the median (minimum–maximum).
C_{max}, maximum plasma concentration; AUC_{last}, area under the concentration-time curve from the time of zero to the last observed time point; AUC_{inf}, AUC from zero to infinity; T_{max}, the time to reach to maximum plasma concentration; $T_{1/2}$, half-life; CL/F, apparent total clearance.
*Number of subjects for the AUC_{inf}, $t_{1/2}$ and CL/F of berberine and epicatechin was 1 in the fed condition and number of subjects for the AUC_{inf}, $t_{1/2}$ and CL/F of epicatechin was 1 in the fasted condition; †Mann-Whitney U test.

DISCUSSION

This study was the first study to evaluate the food effects on the PKs of *Pelargonium sidoides* and *Coptis* with each bioactive compound berberine and epicatechin in Korean healthy subjects. In this study, the systemic exposure of berberine and epicatechin tended to be higher in the fasted condition compared to the fed condition. The T_{max} of berberine and epicatechin and the $t_{1/2}$ of berberine were similar between the treatment groups. Both treatments were well tolerated by the subjects based on the AEs, vital signs, clinical laboratory tests, 12-lead ECGs, and physical exams.

Food can affect the PKs of berberine and epicatechin in various ways such as changing gastrointestinal pH, increasing splanchnic blood flow, or physically or chemically interacting with a drug substance. However, since the median T_{max} of berberine and epicatechin was similar regardless of food consumption, it is thought that the possibility of the food impact on the PKs due to the delay in gastric emptying is low [17].

Berberine has a low bioavailability of far less than 1% in rats resulting from a low intestinal absorption by the P-glycoprotein mediated drug efflux, poor water solubility and extensive intestinal first-pass effect [19]. Berberine is a hydrophilic compound and belongs to biopharmaceutical classification system class III which results in negative food effects through complex combination of factors that influence the *in vivo* dissolution of the drug product or the absorption of the drug substance [18,20]. From a pKa perspective, berberine, a quaternary ammonium salt, is a permanently charged compound and has no ionizable groups. Therefore, there is no change in ionization when gastrointestinal pH increases after food intake, and it is less likely that changes in drug solubility affect the berberine absorption [21].

The flavonoids to which epicatechin belongs are a weak acid of a hydrophobic compound. The ionization of epicatechin would be expected to increase when gastric pH increases by food consumption. Its ionization leads to a decreased extent of absorption into the

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gastrointestinal tract. In addition, the aqueous stability of epicatechin is known which decreases with the rise in pH value [22]. Therefore, the extent of absorption can be limited resulting in rapid hydrolyzation due to a decreased aqueous stability [23].

In general, PK studies on herbal medicines are very difficult to quantify the bioactive substance because of the chemical complexity [24]. As a result, there is very little PK data for many herbal products that are commonly used in clinics and hospitals. In this study, plasma concentrations of berberine and epicatechin were below the limit at various time points in the elimination phase. However, for berberine and epicatechin, the threshold time points below the limit concentration in elimination phase were similar between treatment group, so no additional comparison was conducted through the adjusted AUC_{last} calculation. Furthermore, it was difficult to identify the individual PK profiles including the terminal phase, and for some parameters, the value of one subject represented the average value of the treatment group. Therefore, considering that this study is an exploratory food effect study conducted in parallel design for minimal subjects without considering statistical power, it is necessary to understand the study results in an exploratory aspect. This study is meaningful in terms of generating PK data and information evaluating food effects on the PKs of berberine and epicatechin which is important in designing a dosing regimen for a confirmatory clinical trial and providing information for clinical pharmacology in a clinical setting.

REFERENCES

1. Young EC, Smith JA. Quality of life in patients with chronic cough. Ther Adv Respir Dis 2010;4:49-55.
PUBMED | CROSSREF
2. Kardos P. Management of cough in adults. Breathe 2010;7:122-133.
CROSSREF
3. Knutson D, Braun C. Diagnosis and management of acute bronchitis. Am Fam Physician 2002;65:2039-2044.
PUBMED
4. Lutsenko Y, Bylka W, Matlawska I, Darmohray R. Hedera helix as a medicinal plant. Herba Pol 2010;56:83-96.
5. Kolodziej H, Kayser O, Radtke OA, Kiderlen AF, Koch E. Pharmacological profile of extracts of Pelargonium sidoides and their constituents. Phytomedicine 2003;10 Suppl 4:18-24.
PUBMED | CROSSREF
6. Wang J, Wang L, Lou GH, Zeng HR, Hu J, Huang QW, et al. Coptidis Rhizoma: a comprehensive review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. Pharm Biol 2019;57:193-225.
PUBMED | CROSSREF
7. Janecki A, Conrad A, Engels I, Frank U, Kolodziej H. Evaluation of an aqueous-ethanolic extract from *Pelargonium sidoides* (EPs® 7630) for its activity against group A-streptococci adhesion to human HEp-2 epithelial cells. J Ethnopharmacol 2011;133:147-152.
PUBMED | CROSSREF
8. Miao L, Yun X, Yang X, Jia S, Jiao C, Shao R, et al. An inhibitory effect of Berberine from herbal *Coptis chinensis Franch* on rat detrusor contraction in benign prostatic hyperplasia associated with lower urinary tract symptoms. J Ethnopharmacol 2021;268:113666.
PUBMED | CROSSREF
9. Ghayur MN, Khan H, Gilani AH. Antispasmodic, bronchodilator and vasodilator activities of (+)-catechin, a naturally occurring flavonoid. Arch Pharm Res 2007;30:970-975.
PUBMED | CROSSREF
10. Jeong HW, Hsu KC, Lee JW, Ham M, Huh JY, Shin HJ, et al. Berberine suppresses proinflammatory responses through AMPK activation in macrophages. Am J Physiol Endocrinol Metab 2009;296:E955-E964.
PUBMED | CROSSREF
11. Lou T, Zhang Z, Xi Z, Liu K, Li L, Liu B, et al. Berberine inhibits inflammatory response and ameliorates insulin resistance in hepatocytes. Inflammation 2011;34:659-667.
PUBMED | CROSSREF

12. Sánchez-Mendoza ME, Castillo-Henkel C, Navarrete A. Relaxant action mechanism of berberine identified as the active principle of *Argemone ochroleuca* sweet in guinea-pig tracheal smooth muscle. J Pharm Pharmacol 2008;60:229-236.
PUBMED | CROSSREF

13. Song KJ, Shin YJ, Lee KR, Lee EJ, Suh YS, Kim KS. Expectorant and antitussive effect of *Hedera helix* and *Rhizoma coptidis* extracts mixture. Yonsei Med J 2015;56:819-824.
PUBMED | CROSSREF

14. Volstatova T, Marchica A, Hroncova Z, Bernardi R, Doskocil I, Havlik J. Effects of chlorogenic acid, epicatechin gallate, and quercetin on mucin expression and secretion in the Caco-2/HT29-MTX cell model. Food Sci Nutr 2019;7:492-498.
PUBMED | CROSSREF

15. Ferreira PG, Ferraz AC, Figueiredo JE, Lima CF, Rodrigues VG, Taranto AG, et al. Detection of the antiviral activity of epicatechin isolated from *Salacia crassifolia* (Celastraceae) against Mayaro virus based on protein C homology modelling and virtual screening. Arch Virol 2018;163:1567-1576.
PUBMED | CROSSREF

16. Song JM, Lee KH, Seong BL. Antiviral effect of catechins in green tea on influenza virus. Antiviral Res 2005;68:66-74.
PUBMED | CROSSREF

17. U.S. Food and Drug Administration. Guidance for industry: food-effect bioavailability and fed bioequivalence studies. Silver Spring (MD): FDA; 2002.

18. Radwan A, Amidon GL, Langguth P. Mechanistic investigation of food effect on disintegration and dissolution of BCS class III compound solid formulations: the importance of viscosity. Biopharm Drug Dispos 2012;33:403-416.
PUBMED | CROSSREF

19. Habtemariam S. The quest to enhance the efficacy of berberine for type-2 diabetes and associated diseases: physicochemical modification approaches. Biomedicines 2020;8:90.
PUBMED | CROSSREF

20. Chen W, Miao YQ, Fan DJ, Yang SS, Lin X, Meng LK, et al. Bioavailability study of berberine and the enhancing effects of TPGS on intestinal absorption in rats. AAPS PharmSciTech 2011;12:705-711.
PUBMED | CROSSREF

21. Battu SK, Repka MA, Maddineni S, Chittiboyina AG, Avery MA, Majumdar S. Physicochemical characterization of berberine chloride: a perspective in the development of a solution dosage form for oral delivery. AAPS PharmSciTech 2010;11:1466-1475.
PUBMED | CROSSREF

22. Liu M, Zheng Y, Wang C, Xie J, Wang B, Wang Z, et al. Improved stability of (+)-catechin and (-)-epicatechin by complexing with hydroxypropyl-β-cyclodextrin: Effect of pH, temperature and configuration. Food Chem 2016;196:148-154.
PUBMED | CROSSREF

23. Fleisher D, Johnson KC, Stewart BH, Amidon GL. Oral absorption of 21-corticosteroid esters: a function of aqueous stability and intestinal enzyme activity and distribution. J Pharm Sci 1986;75:934-939.
PUBMED | CROSSREF

24. Alolga RN, Fan Y, Zhang G, Li J, Zhao YJ, Lelu Kakila J, et al. Pharmacokinetics of a multicomponent herbal preparation in healthy Chinese and African volunteers. Sci Rep 2015;5:12961.
PUBMED | CROSSREF