pharmaceutics

Supplementary Material: Clinical Evaluation of Acetaminophen-Galgeuntang Interaction Based on Population Approaches

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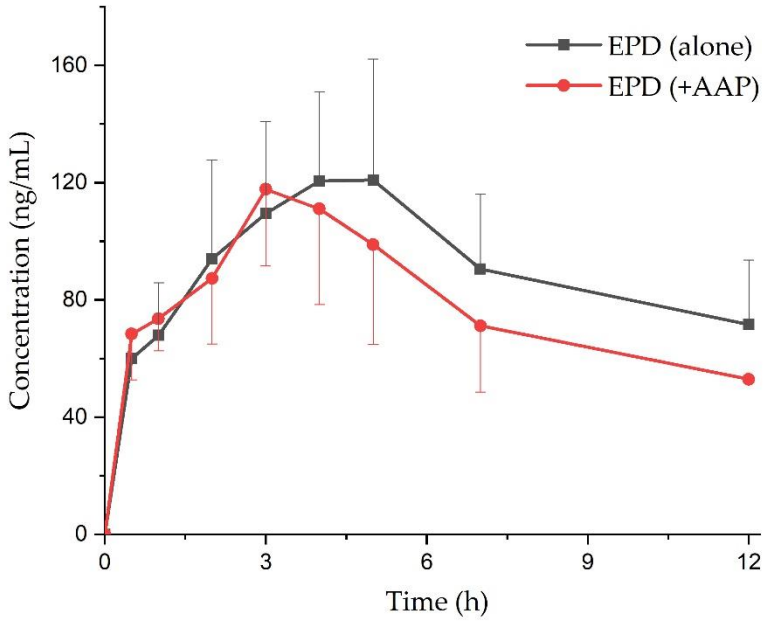

Figure S1. Comparison of plasma concentration-time profiles of ephedrine after administration alone or co-administration with acetaminophen (AAP). Each point represents the mean and standard deviation. EPD, ephedrine.

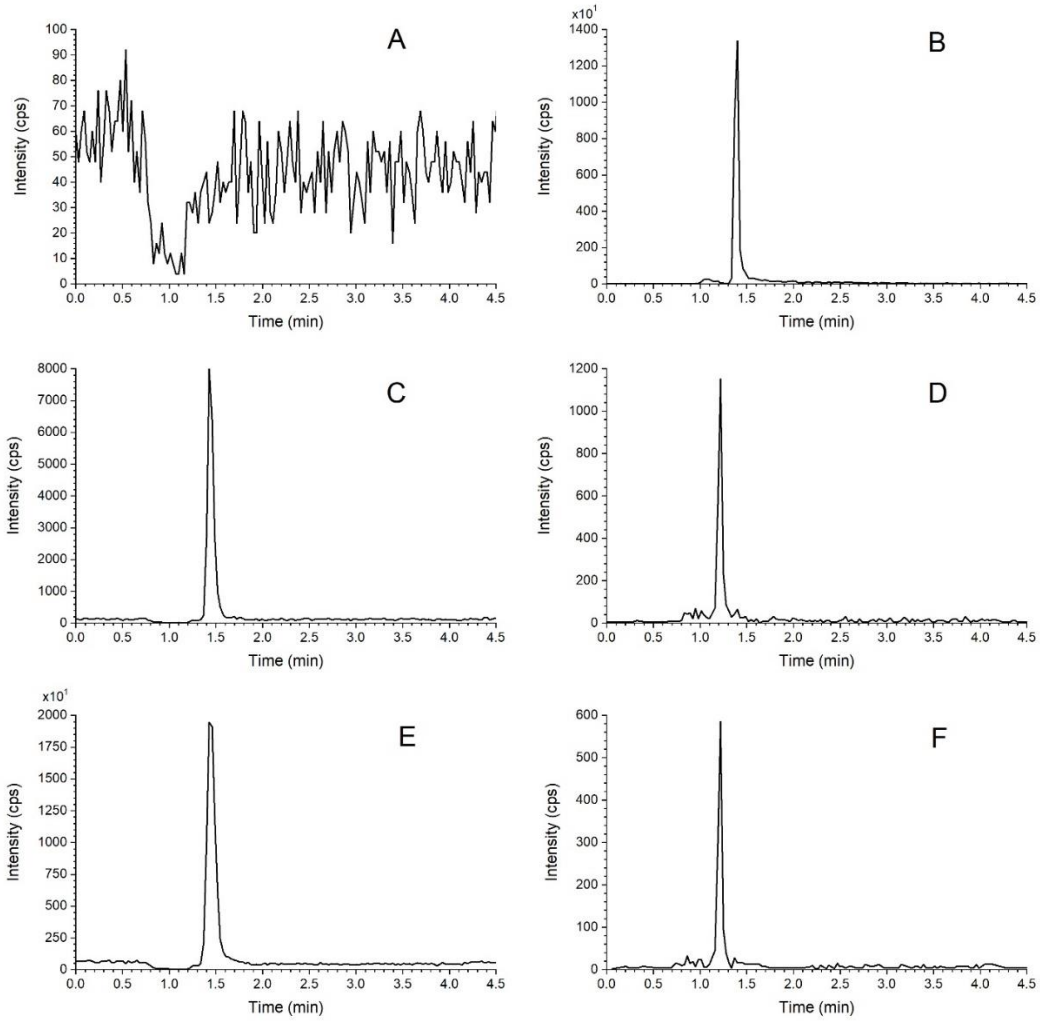

Figure S2. Representative chromatogram of blank plasma (**A**), blank plasma spiked with internal standard (**B**), standard sample of AAP at dose of 2 μg/mL (**C**), standard sample of EPD at dose of 0.5 μg/mL (**D**), real sample of AAP at 3 h after administration combination of AAP and Galgeuntang (GGT) (**E**), real sample of EPD at 3 h after administration combination of AAP and GGT (**F**).

Table S1. Inclusion and exclusion of participants enrolling clinical trial.

Criteria	Contents
Inclusion criteria	1. Men age from 20 to 45 years old 2. Body weight ≥55 kg, and within ±20% IBW [1] (ideal body weight) 3. Subject without any significant chronic disease 4. No pathological conditions at time of screening 5. Adhere the protocol and sign in an informed consent form
Exclusion criteria	1. Inflammatory fever 2. History of clinically significant hepatic, kidney, digestive system, pulmonary, blood, endocrine, urinary, neurology, musculoskeletal, immune, and cardiovascular systems 3. History of gastrointestinal surgery or gastrointestinal disorders which may importantly affect absorption of drugs 4. Aspirin-induced asthma 5. Clinically significant allergies, including GGT components or AAP 6. Clinically significant vital sign: -Systolic blood pressure > 140 or < 100 mmHg -Diastolic blood pressure > 90 or < 60 mmHg -Heart rate ≥ 100 beats/min 7. Clinical laboratory test values are outside the accepted normal range: -AST or ALT ≥ 2 times to the upper limit value -Total bilirubin > 2 times the upper limit value 8. Use of prescription medicines within 14 days or non-prescription medicines within 7 days before dosing 9. History of drug abuse 10. Renal impairment (Creatinine clearance < 50 mL/min) 11. Using drugs which related to inhibition or induction of our drugs within 1 month before dosing 12. Participated in other study within 3 months before dosing 13. Bleeding tendency in blood test 14. History of alcohol, smoking abuse: -Alcohol > 210g/weeks -Smoking ≥ 10 cigarettes/day 15. Donated blood within 2 months; received or had blood transfusion within 1 month before dosing 16. Subjected considered as unsuitable based on medical judgement by investigators

Table S2. Intra-day and inter-day of accuracies and precisions of AAP and EPD.

Compounds	Concentration (ng/mL)	Intra-day		Inter-day	
		Precision (%RSD)	Accuracy (%RE)	Precision (%RSD)	Accuracy (%RE)
Acetaminophen	50	−1.06	6.92	3.94	4.49
	2000	−0.853	5.58	1.17	5.11
	10,000	−0.0405	2.54	−5.21	3.85
Ephedrine	50	8.99	6.44	4.65	3.44
	500	−2.79	3.50	−6.06	6.25
	2500	3.67	3.02	3.07	4.28

RSD: relative standard deviation, RE: relative error.

Table S3. NCA results of PK parameters of EPD.

Parameter	Mean ± SD		*p*-value
	EPD (single) *n* = 12	EPD (+AAP) *n* = 11	
$AUC_{0\text{-}t}$ (ng h/mL)	969 ± 249	833 ± 217	$p > 0.05$
AUC_{inf} (ng h/mL)	1399 ± 496	1206 ± 313	$p > 0.05$
C_{max} (ng/mL)	142 ± 32.6	126 ± 27.3	$p > 0.05$
T_{max} (h)	3.38 ± 1.11	3.55 ± 1.04	$p > 0.05$
$t_{1/2}$ (h)	5.82 ± 2.11	6.01 ± 3.22	$p > 0.05$
CL/*F* (mL/h)	25.1 ± 8.86	28.0 ± 8.14	$p > 0.05$
V/*F* (mL/h)	195 ± 60.7	225 ± 79.7	$p > 0.05$

AUC_{inf}, area under the plasma concentration-time curve from 0 to infinity; C_{max}, maximum observed plasma concentration; T_{max}, time to reach maximum observed concentration; $t_{1/2}$, plasma half-life associated with terminal slope of a semilogarithmic concentration-time curve; *CL*, clearance; *V*, volume of distribution; *F*, bioavailability; SD, standard deviation.

Reference:

1. Syahputra, M.F.; Felicia, V.; Rahmat, R.F.; Budiarto, R. Scheduling Diet for Diabetes Mellitus Patients using Genetic Algorithm. *J. Phys. Conf. Ser.* **2016**, *755*, doi:10.1088/1742-6596/755/1/011001.