

Supplementary Materials: Matrix Effects of the Hydroethanolic Extract of Calyces of *Physalis peruviana* L. on Rutin Pharmacokinetics in Wistar Rats Using Population Modeling

Gina Paola Domínguez Moré, María Isabel Cardona, Paula Michelle Sepúlveda, Sandra Milena Echeverry, Cláudia Maria Oliveira Simões and Diana Marcela Aragón

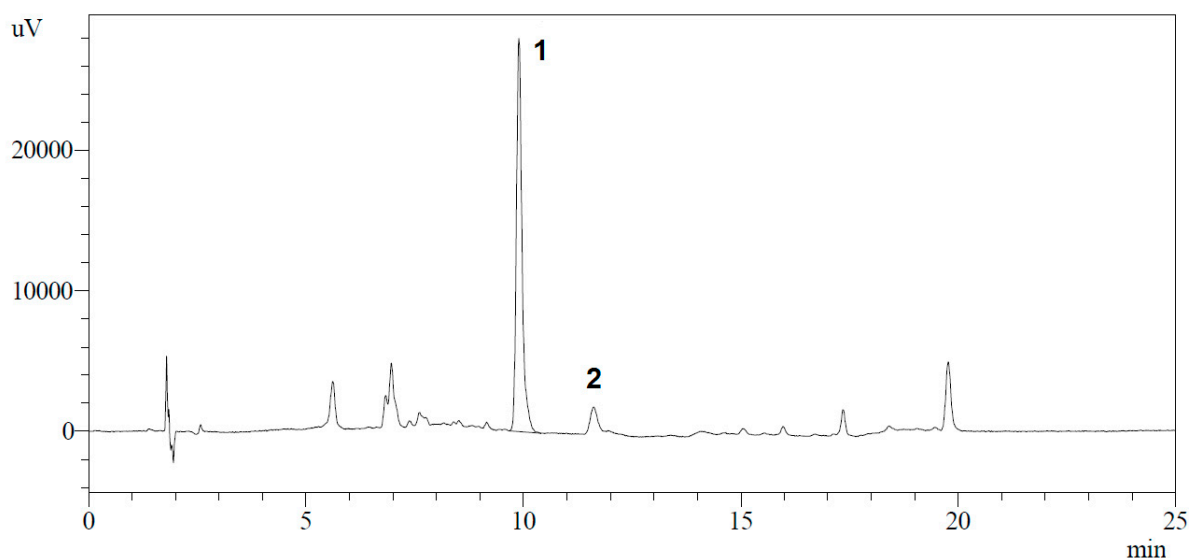


Figure S1. Chromatographic profile of the hydroethanolic extract of calyces from *Physalis peruviana*. **1:** rutin, retention time 9.8 min. **2:** Nicotiflorin, retention time 10.5 min. Column C18 (150 × 3.9 mm, 10 μm), mobile phase with methanol (A) and water, acidified with acetic acid at 0.5%, in gradient from 10 to 80% A, over 25 min at 1 mL/min; column oven at 35°C, detection at 350 nm and injections of 10 μL of the samples diluted in methanol (1 mg/mL) [39].

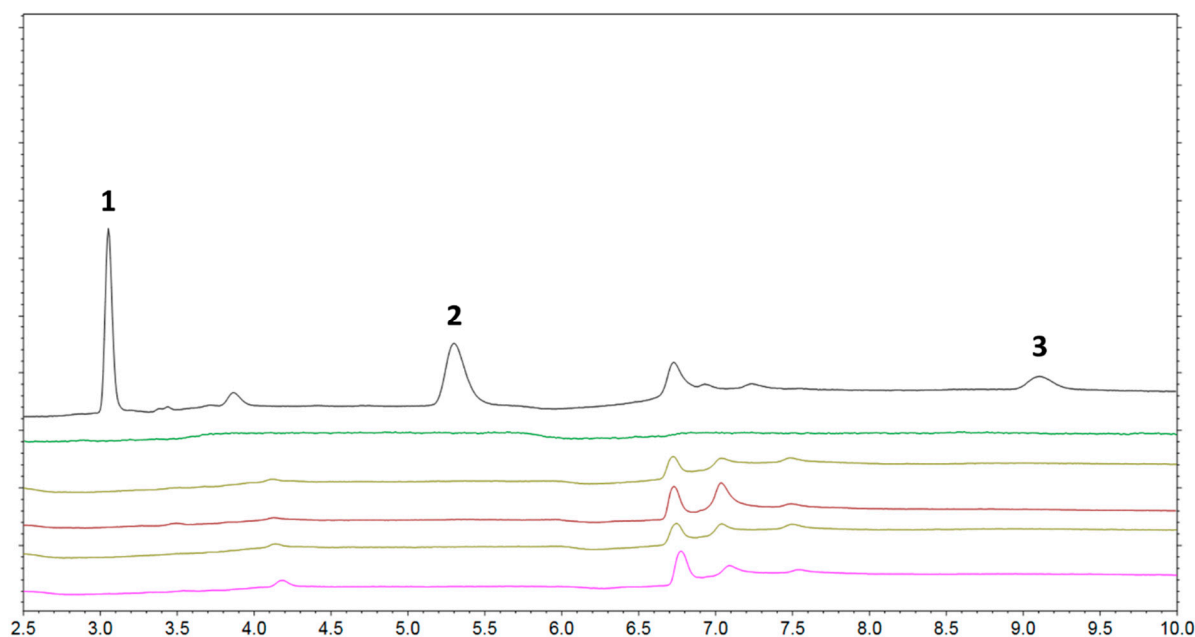


Figure S2. Selectivity and specificity of the bioanalytical method. Colored lines are blank samples from different rats. Black line is blank plasma spiked with rutin (peak 1, 3.1 min) and quercetin (peak 2, 5.4 min) at concentration of 250 ng/mL, the internal standard (IS) chrysin (peak 3, 9.1 min) at concentration of 1000 ng/mL and quercetin-3-*O*-glucuronide for potential interference evaluation. There was not interfering signals for the analytes and IS. Column Kinetex® EVO C18, 2,6 μ m, 100 \times 2.1 mm at 30°C, mobile phase with formic acid 0.1% (A) and acetonitrile acidified with formic acid at 0.5%, in gradient from 85 to 65% A, at 0.5 mL/min. Detection at 260 nm and injections of 6 μ L of the samples. Samples were prepared by protein precipitation with methanol (1:2).

Table S1. Summary of run record for modelling of rutin in intravenously administration experiments.

Run Description		Results			
	Parameter	Value	SE	RSE (%)	
Pure rutin: one compartment model, first order elimination.	V_pop	7.81 e ⁻⁵	6.51 e ⁻⁶	8.33	
	k_pop	1.22	0.0604	4.97	
	AIC: 1656				
Pure rutin: two-compartment model, first order elimination.	V_pop	5.89e ⁻⁵	2.85 e ⁻⁶	4.83	
	k_pop	1.61	0.00181	0.113	
	k12_pop	5.24	1.33	25.4	
	k21_pop	19.4	0.151	0.779	
AIC: 1646					
Pure rutin: selection of model error and final model	V_pop	6.4e ⁻⁵	3.37 e ⁻⁶	5.27	
	k_pop	1.48	0.04	2.69	
	k12_pop	2.5	1.77	8.35	
	k21_pop	16.8	11.7	4.96	
AIC: 1644					
Extract: one compartment model, first order elimination.	V_pop	0.000128	1.08 e ⁻⁵	8.48	
	k_pop	1.8	0.0623	3.45	
AIC: 2478					
Extract: two-compartment model, first order elimination and final model.	V_pop	0.000106	8.49 e ⁻⁶	8.04	
	k_pop	2.18	0.0722	3.31	
	k12_pop	2.3	0.0622	20.6	
	k21_pop	13	0.00193	0.00935	
AIC: 2470					
Pure rutin and extract model: model of covariate 1.	V_pop	5.9 e ⁻⁵	1.12 e ⁻⁵	19.1	
	beta_V_tCOVARI-ATE_2_G_EXT	0.458	0.126	27.5	
	k_pop	1.58	0.258	16.3	
	beta_k_tCOVARI-ATE_2_G_EXT	0.404	0.0587	14.5	
	k12_pop	2.62	2.73	104	
	k21_pop	9.67	3.6	37.2	
AIC: 4197					
Pure rutin and extract model: final model.	V_pop	6.46 e ⁻⁵	6.62 e ⁻⁶	10.2	
	beta_V_tCOVARI-ATE_2_G_EXT	0.478	0.128	26.8	
	k_pop	1.47	0.0812	5.54	
	beta_k_tCOVARI-ATE_2_G_EXT	0.395	0.0622	15.8	
	k12_pop	2.6	1.1	42.3	
	k21_pop	13.6	4.37	32.2	
AIC: 4121					

Pop: population parameter. S.E.: standard error. R.S.E.: relative standard error. V: volume of the central compartment, k: first order rate constant of elimination, k12 rate constant of drug distribution from central to the peripheral compartment, k21 rate constant of drug distribution from peripheral to central compartment, β : variability due to significant covariate, GEXT: covariate extract.

Table S2. Summary of run record for modelling of quercetin in oral administration experiments.

Run Description	Results			
	Parameter	Value	SE	RSE (%)
Pure rutin: one compartment model, two first order absorption, first order elimination.	ka1_pop	0.992	0.0676	6.81
	ka2_pop	3.33	1.67	50.2
	F1_pop	0.336	0.0229	6.79
	Tlag2_pop	3.93	0.0351	0.892
	V_pop	0.0868	0.00204	2.35
	k_pop	0.241	0.00989	4.1
AIC: 1067				
Pure rutin: two-compartment model, two first order absorption, first order elimination.	Parameter	Value	SE	RSE (%)
	ka1_pop	0.605	0.107	17.6
	ka2_pop	1.1	0.241	21.9
	F1_pop	0.358	0.0268	7.49
	Tlag2_pop	3.85	0.0273	0.707
	V_pop	0.0566	0.00865	15.3
	k_pop	0.344	0.0581	16.9
k12_pop	0.232	0.0912	39.2	
k21_pop	0.336	0.137	40.8	
AIC: 1047				
Pure rutin: evaluation of random effects.	Parameter	Value	SE	RSE (%)
	ka1_pop	0.614	0.0373	6.07
	ka2_pop	2.35	0.502	21.4
	F1_pop	0.36	0.0257	7.15
	Tlag2_pop	3.94	0.0104	0.265
	V_pop	0.0562	0.00262	4.66
	k_pop	0.352	0.0192	5.45
	k12_pop	0.324	0.0808	25
k21_pop	0.659	0.143	21.6	
AIC: 1037				
Pure rutin: selection of model error and final model	Parameter	Value	SE	RSE (%)
	ka1_pop	0.277	0.136	49
	ka2_pop	0.545	0.145	26.7
	F1_pop	0.411	0.0684	16.7
	Tlag2_pop	3.86	0.0312	0.809
	V_pop	0.0284	0.0115	40.4
	k_pop	0.707	0.29	41
	k12_pop	0.391	0.0908	23.2
k21_pop	0.29	0.132	45.5	
AIC: 1034				
Extract: one compartment model, two first order absorption, first order elimination.	Convergence did not reach.			
Extract: two-compartment model, two first order absorption, first order elimination.	Parameter	Value	SE	RSE (%)
	ka1_pop	1.28	0.176	13.8
	ka2_pop	0.485	0.133	27.4
	F1_pop	0.62	0.0494	7.96
	Tlag2_pop	2.3	0.371	16.1
V_pop	0.0114	0.000797	7	

Run Description		Results		
	k_pop	0.224	0.0216	9.65
	k12_pop	0.776	0.349	45
	k21_pop	0.543	0.0248	4.56
AIC: 1699				
Extract: initial selection of covariates	Parameter	Value	SE	RSE (%)
	ka1_pop	0.803	0.159	19.8
	beta_ka1_COVARIATE_D2	1.08	0.203	18.8
	beta_ka1_COVARIATE_D3	1.8	0.219	12.2
	ka2_pop	0.469	0.144	30.8
	F1_pop	0.616	0.0456	7.4
	Tlag2_pop	4.46	0.601	13.5
	beta_Tlag2_COVARIATE_D2	-0.799	0.162	20.3
	beta_Tlag2_COVARIATE_D3	-1.78	0.228	12.8
	V_pop	0.00814	0.0017	20.9
	beta_V_COVARIATE_D2	0.782	0.153	19.5
	beta_V_COVARIATE_D3	1.65	0.16	9.67
	k_pop	0.328	0.0801	24.4
	beta_k_COVARIATE_D2	-0.69	0.197	28.6
	beta_k_COVARIATE_D3	-2.2	0.247	11.2
	k12_pop	0.308	0.0816	26.5
	k21_pop	0.347	0.104	30.1
AIC: 1575				
Extract: evaluation of random effects.	Parameter	Value	SE	RSE (%)
	ka1_pop	0.837	0.146	17.4
	beta_ka1_COVARIATE_D2	1.03	0.182	17.7
	beta_ka1_COVARIATE_D3	1.64	0.193	11.8
	ka2_pop	0.495	0.123	24.9
	F1_pop	0.615	0.0398	6.48
	Tlag2_pop	4.25	0.701	16.5
	beta_Tlag2_COVARIATE_D2	-0.756	0.174	23.1
	beta_Tlag2_COVARIATE_D3	-1.16	0.228	19.7
	V_pop	0.0085	0.0015	17.6
	beta_V_COVARIATE_D2	0.737	0.131	17.9
	beta_V_COVARIATE_D3	1.55	0.138	8.91
	k_pop	0.297	0.0674	22.7
	beta_k_COVARIATE_D2	-0.665	0.187	28.1
	beta_k_COVARIATE_D3	-2.06	0.243	11.8
	k12_pop	0.314	0.0747	23.8
	k21_pop	0.301	0.0927	30.8
AIC: 1566				
Extract: selection of model error and final model	Parameter	Value	SE	RSE (%)
	ka1_pop	0.833	0.109	13.1
	beta_ka1_COVARIATE_D2	0.974	0.186	19.1
	beta_ka1_COVARIATE_D3	1.63	0.178	11
	ka2_pop	0.487	0.105	21.5
	F1_pop	0.617	0.033	5.35
	Tlag2_pop	4.15	0.699	16.8
	beta_Tlag2_COVARIATE_D2	-0.73	0.168	23
	beta_Tlag2_COVARIATE_D3	-1.18	0.24	20.3
	V_pop	0.00837	0.000866	10.4
	beta_V_COVARIATE_D2	0.71	0.0991	14
	beta_V_COVARIATE_D3	1.55	0.0984	6.35
	k_pop	0.301	0.0403	13.4
	beta_k_COVARIATE_D2	-0.604	0.161	26.7
	beta_k_COVARIATE_D3	-2.04	0.188	9.21
	k12_pop	0.343	0.0862	25.1
	k21_pop	0.325	0.0937	28.8

Run Description		Results		
		0		
AIC: 1549				
Pure rutin and extract model: model of covariate 1.	Parameter	Value	SE	RSE (%)
	ka1_pop	0.133	0.0191	14.3
	beta_ka1_tCOVARI-ATE_1_G_D3	-0.103	0.189	184
	beta_ka1_tCOVARI-ATE_1_G_D4	1.75	0.158	9.02
	beta_ka1_tCOVARI-ATE_1_G_D5	2.91	0.16	5.49
	beta_ka1_tCOVARI-ATE_1_G_D6	3.51	0.19	5.41
	ka2_pop	0.409	0.121	29.6
	F1_pop	0.559	0.0584	10.4
	Tlag2_pop	3.85	0.0489	1.27
	beta_Tlag2_tCOVARI-ATE_1_G_D3	0.0144	0.00591	40.9
	beta_Tlag2_tCOVARI-ATE_1_G_D4	0.105	0.11	105
	beta_Tlag2_tCOVARI-ATE_1_G_D5	-0.687	0.0613	8.92
	beta_Tlag2_tCOVARI-ATE_1_G_D6	-1.14	0.282	24.6
	V_pop	0.0153	0.00161	10.5
	beta_V_tCOVARI-ATE_1_G_D3	0.00836	0.147	1.76 e ⁺³
	beta_V_tCOVARI-ATE_1_G_D4	-0.737	0.119	16.2
	beta_V_tCOVARI-ATE_1_G_D5	0.0888	0.124	140
	beta_V_tCOVARI-ATE_1_G_D6	0.922	0.12	13
	k_pop	1.25	0.107	8.53
	beta_k_tCOVARI-ATE_1_G_D3	-5.64 e ⁻⁵	0.112	1.99 e ⁺⁵
	beta_k_tCOVARI-ATE_1_G_D4	-1.26	0.106	8.37
	beta_k_tCOVARI-ATE_1_G_D5	-2.01	0.123	6.13
	beta_k_tCOVARI-ATE_1_G_D6	-3.41	0.317	9.31
k12_pop	0.289	0.171	59.1	
k21_pop	0.272	0.202	74.2	
AIC: 2652				
Pure rutin and extract model: final model.	Parameter	Value	SE	RSE (%)
	ka1_pop	0.104	0.0129	12.5
	beta_ka1_tCOVARI-ATE_1_G_D2	0.281	0.167	59.6
	beta_ka1_tCOVARI-ATE_1_G_D4	1.94	0.166	8.54
	beta_ka1_tCOVARI-ATE_1_G_D5	3.15	0.176	5.59
	beta_ka1_tCOVARI-ATE_1_G_D6	3.77	0.175	4.64
	ka2_pop	0.411	0.0686	16.7
	F1_pop	0.565	0.0275	4.87
	Tlag2_pop	3.91	0.021	0.538

Run Description	Results		
beta_Tlag2_tCOVARI- ATE_1_G_D2	-0.0177	0.00556	31.3
beta_Tlag2_tCOVARI- ATE_1_G_D4	0.149	0.0936	63
beta_Tlag2_tCOVARI- ATE_1_G_D5	-0.695	0.0595	8.56
beta_Tlag2_tCOVARI- ATE_1_G_D6	-1.17	0.254	21.7
V_pop	0.0132	0.00114	8.68
beta_V_tCOVARI- ATE_1_G_D2	0.251	0.0951	37.8
beta_V_tCOVARI- ATE_1_G_D4	-0.645	0.105	16.4
beta_V_tCOVARI- ATE_1_G_D5	0.245	0.118	48.2
beta_V_tCOVARI- ATE_1_G_D6	1.09	0.101	9.25
k_pop	1.42	0.119	8.35
beta_k_tCOVARI- ATE_1_G_D2	-0.225	0.0824	36.6
beta_k_tCOVARI- ATE_1_G_D4	-1.3	0.144	11.2
beta_k_tCOVARI- ATE_1_G_D5	-2.13	0.181	8.49
beta_k_tCOVARI- ATE_1_G_D6	-3.57	0.231	6.47
k12_pop	0.279	0.0802	28.8
k21_pop	0.268	0.107	39.9

AIC: 2648

Pop: population parameter. S.E.: standard error. R.S.E.: relative standard error. ka1: first order absorption rate constant from first site, ka2: first order absorption rate constant from second site, F1: absorbed fraction from first site, Tlag2: delay for second absorption, V: volume of the central compartment, k: first order rate constant of elimination, k12 rate constant of drug distribution from central to the peripheral compartment, k21 rate constants of drug distribution from peripheral to central compartment, β : variability due to significant covariate, G_D2: covariate pure rutin dose 75 mg/kg; G_D4, G_D5, G_6: covariate extract doses 500, 750 and 1000 mg/kg respectively.