Supplementary
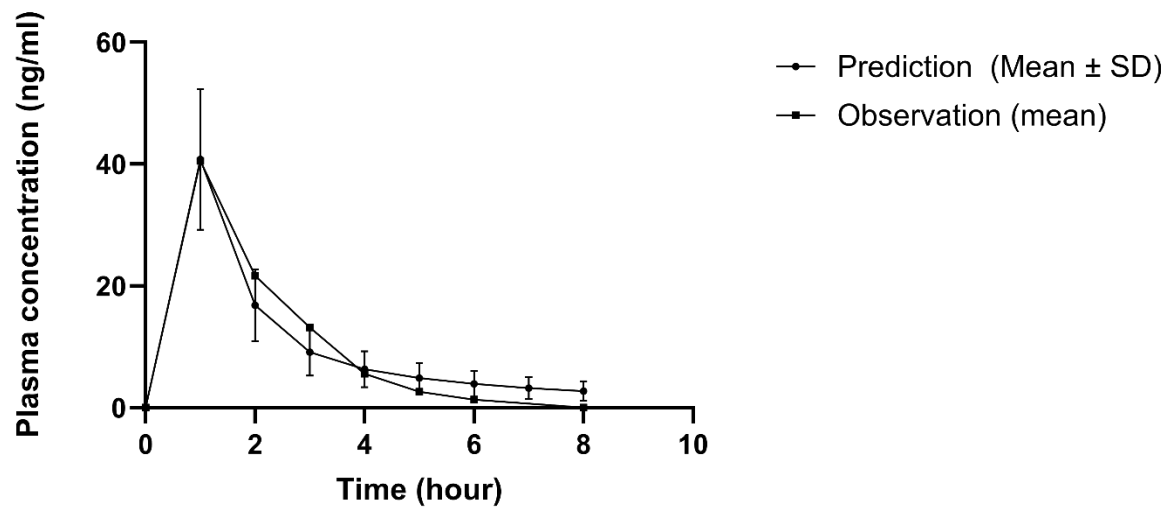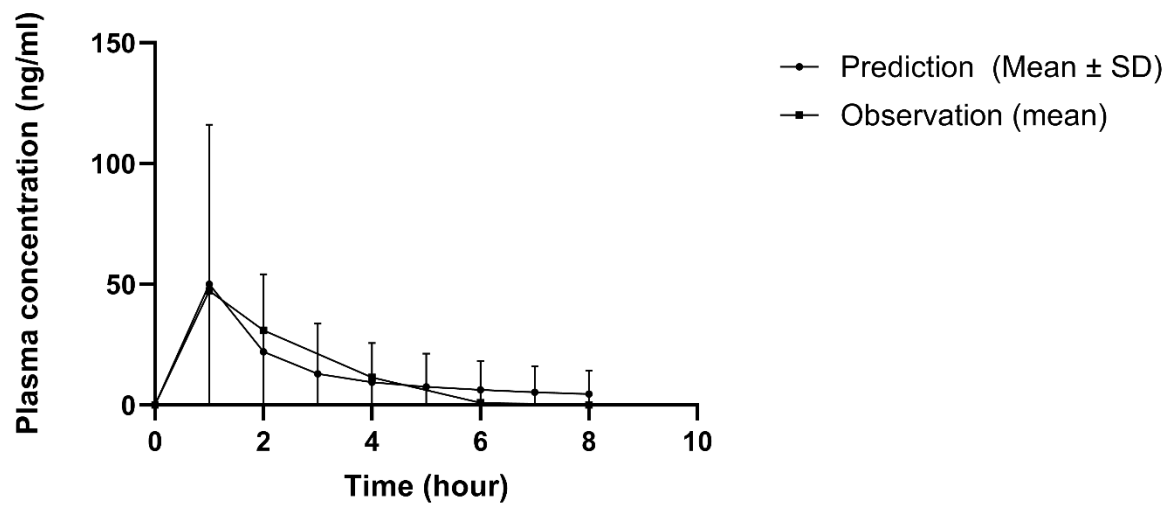
Figure S1 A comparison of atractylodin plasma concentration-time profiles following a single dose of 1,000 mg of *Atractylodes Lancea* (Thunb) DC on day 1 between predicted values and clinical data [5].

Figure S2 A comparison of atractylodin plasma concentration-time profiles following multiple doses of 1,000 mg of *Atractylodes Lancea* (Thunb) DC on day 1 between predicted values and clinical data [5].

Figure S3 A comparison of atractylodin plasma concentration-time profiles following multiple doses of 1,000 mg of *Atractylodes Lancea* (Thunb) DC on day 21 between predicted values and clinical data [5].
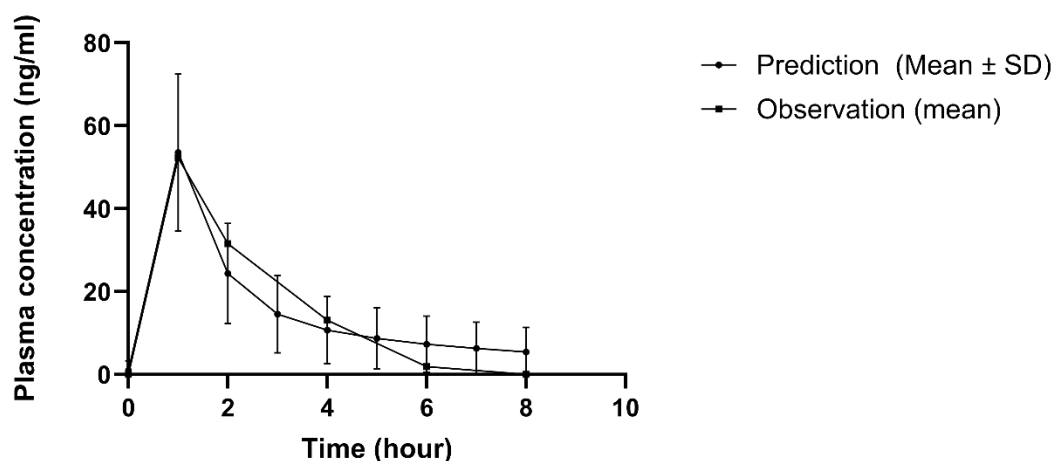
Table S1. Model parameters

Number	Parameter	Value	Reference
1	Fraction of unbound drug (f_u)	0.039	In house
2	pKa	9.63	In house
3	Log D	4.91	Pub-chem
4	Blood-to-plasma partition ratio (R_{bp})	1.03	In house
5	PSA	13.1	Pub-Chem
6	HBD	1	Pub-Chem
7	Absolute bioavailability (F_{bio})	0.8	1
8	Clearance *in vivo* (L/h/kg)	6.26	1
9	Solubility (µg/ml) (PBS pH 6.8, SIF)	0.11±0.003	In house

Table S2. A statistical analysis of circulating cytokines following successive doses of 1,000 mg of AL administered for 21 days

Cytokines	0 hr. versus 24 hr.	0 hr. versus 48 hr.	0 hr. versus day 7	0 hr. versus day 14
Treated group				
IL-2	P=0.2121*	P=0.306*	P<0.0001*	P<0.001*
IL-4	P=0.2524*	P=0.7948*	P=0.0002*	P=0.0007*
IL-6	P=0.0637*	P=0.0826*	P=0.0353*	P=0.1303*
IL-10	P=0.9853 (t=0.018, df=19)	P=0.87 (t=0.164, df=19)	P=0.0032 (t=3.378, df=19)	P=0.0566 (t=2.03, df=19)
IL-17A	P=0.0002*	P=0.0188*	P=0.0008	P=0.0148
TNF-α	P=0.063 (t=1.972, df=19)	P=0.529 (t=0.64, df=19)	P<0.0001 (t=4.94, df=19)	P=0.164 (t=1.448, df=19)
IFN-γ	P=0.044 (t=2.154, df=19)	P=0.0362*	P=0.1211*	P=0.0148 (t=2.68, df=19)
Untreated (Placebo) group				
IL-2	P=0.875*	P=0.625*	P=0.125*	P=0.125*
IL-4	P=0.524 (t=0.72, df=3)	P=0.834 (t=0.23, df=3)	P=0.07 (t=2.76, df=3)	P=0.07 (t=2.76, df=3)

IL-6	P=0.145 (t=1.95, df=3)	P=0.35 (t=1.13, df=3)	P=0.11 (t=2.22, df=3)	P=0.543 (t=0.69, df=3)
IL-10	P=0.375*	P=0.25*	P=0.125*	P=0.625*
IL-17A	P=0.875*	P=0.5*	P=0.875*	P=0.125*
TNF-α	P=0.81 (t=0.26, df=3)	P=0.23 (t=1.51, df=3)	P=0.123 (t=2.59, df=2)	P=0.24 (t=1.47, df=3)
IFN-γ	P=0.88 (t=0.156, df=3)	P=0.28 (t=1.32, df=3)	P<0.0001 (t=96.85, df=3)	P=0.28 (t=1.32, df=3)

*Wilcoxon matched-pairs signed rank test; AL: Atractylodes Lancea (Thunb) D.C.; IL: interleukin; IFN-γ: interferon-gamma; TNF-α: tumor-necrosis factor alpha

Table S3. A statistical analysis of peripheral blood immune cells, SII index, NLR, LMR, PLR, and SII index following daily doses of 1,000 mg of AL administered for 21 days.

Treated group								
Peripheral blood immune cells	0hr versus 24hr	0hr versus 48hr	0hr versus day 4	0hr versus day 7	0hr versus day 14	0hr versus day 21	0hr versus day 22	0hr versus day 23
Lymphocytes	P=0.045 (t=2.15, df=18)	P=0.056 (t=2.04, df=18)	NA	P=0.023*	P=0.004 (t=3.29, df=18)	P=0.01 (t=2.87, df=18)	P=0.0008 (t=4.02, df=18)	P=0.06 (t=2.01, df=18)
T cells	P<0.0001 (t=5.74, df=18)	P=0.024 (t=2.47, df=18)	NA	P<0.0001 (t=6.16, df=18)	P<0.0001 (t=7.37, df=18)	P<0.0001 (t=5.34, df=18)	P=0.0013 (t=3.81, df=18)	P<0.0001 (t=6.39, df=18)
B cells	P<0.0001 (t=6.29, df=18)	P=0.056 (t=2.04, df=18)	NA	P<0.0001 (t=8.51, df=18)	P<0.0001 (t=7.57, df=18)	P=0.168 (t=1.44, df=18)	P=0.008 (t=2.97, df=18)	P=0.001 (t=3.88, df=18)
NK cells	P<0.0001 (t=13.49, df=18)	P<0.0001 (t=5.17, df=18)	NA	P<0.0001 (t=15, df=18)	P<0.0001 (t=13.18, df=18)	P=0.0005 (t=4.28, df=18)	P<0.0001 (t=10.51, df=18)	P<0.0001 (t=9.03, df=18)
CD4+	P<0.0001 (t=10.84, df=18)	P<0.0001 (t=9.47, df=18)	NA	P=0.0002 (t=4.75, df=18)	P=0.13 (t=1.58, df=18)	P<0.0001 (t=6.23, df=18)	P<0.0001 (t=5.27, df=18)	P=0.0001 (t=4.82, df=18)
CD8+	P=0.0012 (t=3.83, df=18)	P=0.112 (t=1.67, df=18)	NA	P=0.08 (t=1.83, df=18)	P=0.0006 (t=4.13, df=18)	P<0.0001 (t=5.05, df=18)	P=0.85 (t=0.18, df=18)	P=0.028 (t=2.40, df=18)
CD4+/CD8+ ratios	P=0.036*	P=0.59*	NA	P=0.19*	P=0.26*	P=0.08*	P=0.0008**	P=0.08*
NLR	NA	NA	P=0.26 (t=1.16, df=19)	NA	NA	NA	P=0.17 (t=1.42, df=18)	NA
LMR	NA	NA	P=0.014 (t=2.7	NA	NA	NA	P=0.11 (t=1.69, df=18)	NA

			0, df=19)					
PLR	NA	NA	P=0.39*	NA	NA	NA	P=0.59*	NA
SII index	NA	NA	P=0.39*	NA	NA	NA	P>0.999*	NA
Untreated (Placebo) group								
Lymphocytes	P=0.97 (t=0.04, df=3)	P=0.98 (t=0.03, df=3)	NA	P=0.68 (t=0.45, df=3)	P=0.61 (t=0.57, df=3)	P=0.61 (t=0.57, df=3)	P=0.70 (t=0.41, df=3)	P=0.12 (t=2.15, df=3)
T cells	P=0.41 (t=1.03, df=2)	P=0.74 (t=0.37, df=2)	NA	NA	P=0.23 (t=1.68, df=2)	P=0.028 (t=5.78, df=2)	P=0.004 (t=14.90, df=2)	P=0.007 (t=11.55, df=2)
B cells	P=0.036 (t=3.61, df=3)	P=0.22 (t=1.54, df=3)	NA	P=0.66 (t=0.48, df=3)	P=0.83 (t=0.23, df=3)	P=0.39 (t=0.99, df=3)	P=0.085 (t=2.53, df=3)	P=0.047 (t=3.25, df=3)
NK cells	P=0.04 (t=3.5, df=3)	P=0.04 (t=3.5, df=3)	NA	P=0.002 (t=10.04, df=3)	P=0.018 (t=4.68, df=3)	P=0.0027 (t=9.17, df=3)	P=0.0003 (t=20.14, df=3)	P=0.0007 (t=14.89, df=3)
CD4+	P=0.087 (t=2.51, df=3)	P=0.26 (t=1.34, df=3)	NA	P=0.004 (t=7.8, df=3)	P=0.02 (t=4.37, df=3)	P=0.0018 (t=10.52, df=3)	P=0.001 (t=12.31, df=3)	P=0.0003 (t=18.91, df=3)
CD8+	P=0.35 (t=1.10, df=3)	P=0.45 (t=0.86, df=3)	NA	P=0.56 (t=0.65, df=3)	P=0.65 (t=0.49, df=3)	P=0.044 (t=3.36, df=3)	P=0.33 (t=1.14, df=3)	P=0.004 (t=8.02, df=3)
CD4+/CD8+ ratio	P=0.40 (t=0.97, df=3)	P=0.52 (t=0.73, df=3)	NA	P=0.37 (t=1.06, df=3)	P=0.44 (t=0.89, df=3)	P=0.27 (t=1.34, df=3)	P=0.33 (t=1.17, df=3)	P=0.41 (t=0.96, df=3)
NLR	NA	NA	P=0.83 (t=0.24, df=3)	NA	NA	NA	P=0.25*	NA
LMR	NA	NA	P=0.80 (t=0.27, df=3)	NA	NA	NA	P=0.047 (t=3.24, df=3)	NA
PLR	NA	NA	P=0.77 (t=0.31, df=3)	NA	NA	NA	P=0.42 (t=0.94, df=3)	NA
SII index	NA	NA	P=0.787 (t=0.36, df=3)	NA	NA	NA	P=0.27 (t=1.35, df=3)	NA

*Wilcoxon matched-pairs signed rank test; LMR: Lymphocyte-to-monocyte Ratio; NA: Not applicable; NK: Natural Killer; NLR: Neutrophil-to-lymphocyte Ratio; PLR: Platelet-to-lymphocyte Ratio; SII index: systemic inflammatory-immune response index.

Table S4. Model validation

Number	Parameter	AAFEs
All Group		
1	AUC	1.10
2	C_{max}	1.06
3	V_z/F	1.34
4	CL/F	1.13
5	$T_{1/2}$ (h)	1.22
AAFEs (Group 1; Day 1)	1.04	
Group 1 (Day 1)		
6	AUC	1.02
7	C_{max}	1.14
8	V_z/F	1.02
9	CL/F	1.03
10	$T_{1/2}$	1.00
Group 2 (Day 1)		
11	AUC	1.19
12	C_{max}	1.03
13	V_z/F	1.49
14	CL/F	1.28
15	$T_{1/2}$	1.27
AAFEs (Group 2; Day 1)	1.24	
Group 2 (Day 21)		
16	AUC	1.11
17	C_{max}	1.00
18	V_z/F	1.60
19	CL/F	1.22
20	$T_{1/2}$	1.42
AAFEs (Group 2; Day 21)	1.25	
AAFEs (All)	1.17	

AUC: area under the plasma concentration-time curve; C_{max}: maximum plasma concentration; Vz/F: volume of distribution; CL/F: apparent clearance; T1/2: terminal half-life.