Supplemental material

Table S1. The lysis spectrum of five phages in the cocktail

Strains	Accession No.	Antibiotic Resistance*[1]	C1	S19cd*[2]	143_2	N2	C6
E.coli 11	MH671408	AMP, TE					
E.coli 12	MH671409	AMP, TE, C, CN			√		
E.coli 13	MH671410	AMP, TE, C, CN, ENR, EFT			√		√
E.coli 14	MH671411	AMP, TE, C, CN, ENR, EFT					
E.coli 15	MH671412	AMP, TE, C					
E.coli 22	MH671413	AMP, TE, C, CN			√	√	√
E.coli 24	MH671414	AMP, TE, C, CN, ENR					
E.coli 31	MH671415	AMP, TE, C					
E.coli 33	MH671416	AMP, TE, ENR	√				
E.coli 34	MH671417	AMP, TE, C					
E.coli 36	MH671419	AMP, TE, C, ENR, EFT					
E.coli 37	MH671420	None					
E.coli 38	MH671421	AMP, TE, EFT			√	√	
E.coli 41	MH671422	AMP, TE, CN, ENR					
E.coli 42	MH671423	AMP, TE, C, CN	√				
E.coli 44	MH671425	AMP, TE, C, CN		√			√
E.coli 45	MH671426	AMP, TE, C, CN, ENR					√
E.coli 46	MH671427	AMP, TE, C			√		
E.coli 47	MH671428	AMP, TE, CN, EFT					
E.coli 51	MH671429	AMP, TE, C					√
E.coli 52	MH671430	AMP, TE, C, CN, ENR					
E.coli 54	MH671431	AMP, TE, C, CN					
E.coli 56	MH671432	AMP, TE, C					
E.coli 57	MH671433	AMP, TE, C, CN, ENR			√		
E.coli 58	MH671434	AMP, TE, C, CN				√	
E.coli 61	MH671435	AMP, TE, C, ENR					
E.coli 62	MH671436	AMP, TE, CN, ENR			√		
E.coli 63	MK156384	AMP, TE, C, CN					
E.coli 71	MH671437	AMP, TE, C, CN, ENR					
E.coli 72	MH671438	AMP, TE, C, CN, ENR, EFT			√		
E.coli 73	MH671439	AMP, TE, C, CN, ENR					
E.coli 81	MH671440	AMP, TE, CN			√		
E.coli 82	MH671441	AMP, TE, CN, ENR					
E.coli 83	MH671442	AMP, TE, C, CN, ENR					
E.coli 84	MH671443	AMP, TE, CN					
E.coli 85	MH671444	AMP, TE, CN, ENR					
E.coli 86	MH671445	AMP, TE, C				√	√
E.coli 87	MH671446	AMP, TE, CN, ENR					
E.coli 91	MH671447	AMP, TE, CN			√		

E.coli 94	MH671448	AMP, TE, C, CN						
E.coli 95	MH671449	AMP, TE, CN						
ETEC 101	MH671450	AMP, TE, C						
ETEC 102	MH671451	TE						
ETEC 103	MH671452	AMP, TE, C, CN, ENR						
ETEC 104	MH671453	AMP, TE				√	√	√
ETEC 105	MH671454	TE, C, CN, ENR						
ETEC 106	MK615932	None					√	√
E.coli 121	MH671455	AMP, TE, CN, ENR				√		
E.coli 122	MH671456	AMP, TE, C, CN, EFT	√					
E.coli 123	MH671457	AMP, TE, C						
E.coli 131	MH671458	AMP, TE, C, CN, EFT	√					
E.coli 132	MH671459	AMP						
E.coli 133	MH671460	AMP, TE, C, CN, ENR						
E.coli 141	MH671461	AMP, C						
E.coli 142	MH671462	AMP, TE, C, CN, ENR						
E.coli 143	MH671463	AMP, TE, C, CN				√		√
E.coli 145	MH671465	AMP, TE, C, CN, EFT	√					
E.coli 151	MH671466	AMP, TE, C, ENR, EFT						
E.coli 156	MH671467	AMP						
E.coli 161	MH671468	CN						
E.coli 162	MH671469	AMP, TE, C, CN, ENR				√	√	
E.coli 164	MH671470	AMP, TE, C, CN, EFT	√					
E.coli 171	MH671471	AMP, TE, C, CN, ENR						
E.coli 172	MH671472	AMP, TE, C			√	√		√
E.coli 173	MH671473	AMP, TE, C, EFT						
E.coli 174	MH671474	AMP, TE, CN						
E.coli 181	MH671475	AMP, TE, C, CN, ENR				√		
E.coli 182	MH671476	AMP, TE, C						
E.coli 191	MH671477	AMP, TE, C, CN				√	√	
E.coli 192	MH671478	AMP, TE, C, CN, EFT	√			√		
E.coli 193	MH671479	AMP, TE, C				√		
E.coli 202	MH671481	AMP, TE, C, ENR						
E.coli 203	MH671482	AMP, TE, C, ENR, EFT						
E.coli 211	MH671483	AMP, TE						
E.coli 212	MH671484	AMP, TE, CN, ENR						
E.coli 231	MH671486	TE, C, CN, ENR, EFT						
E.coli 232	MH671487	AMP, TE, C, CN, ENR						
E.coli 233	MH671488	AMP, TE, C, CN, ENR, EFT						
E.coli 234	MH671489	AMP, TE, C						
E.coli 235	MH671490	AMP, TE, C					√	
E.coli 236	MH671491	AMP, TE, C, ENR, EFT				√		
E.coli 237	MH671492	AMP, TE, C, ENR, EFT				√	√	√

E.coli 241	MH671493	AMP, TE, C, CN, ENR			√
E.coli 242	MH671494	AMP, TE, C, ENR, EFT	√	√	√
E.coli 243	MH671495	AMP, TE, C			
E.coli 244	MH671496	AMP, TE			
E.coli 245	MH671497	AMP, TE, C, CN, ENR			
E.coli W1	MN086362	AMP, TE, C, CN, ENR, EFT			
E.coli W3	MN086363	AMP, TE, C, CN, ENR, EFT			
E.coli W5	MN086364	AMP, TE, C, CN, ENR, EFT	√		

Note: *1, The antibiotics used for resistance tests were gentamicin (CN), ampicillin (AMP), ceftiofur (EFT), tetracycline (TE), chloramphenicol (C) and enoxacin (ENR); *2, S19cd can also infect two pathogenic bacterial strains (ATCC 13312 and CICC 21493) of *Salmonella enterica* serovar Choleraesuis.

Table S2. Effects of phage cocktail on the growth performance of piglets

Indexes	CON	Phage	*P*-value
Initial body weight (kg)	6.26±0.11	6.56±0.18	0.190
Terminal body weight (kg)	14.23±0.36	15.05±0.50	0.212
ADG (g/d)	394.25±14.41	424.58±20.19	0.249
ADFI (g/d)	640.30±70.02	731.19±55.31	0.332
Feed intake/Gain	1.71±0.07	1.76±0.08	0.687

Table S3. Effects of phage cocktail on the serum biochemical indices of piglets

Indexes	Day 11			Day 21		
	CON	Phage	*P*-value	CON	Phage	*P*-value
GLU (mmol/L)	5.68±0.31	4.31±0.74	0.131	5.76±0.58	6.60±0.57	0.327
ALB (g/L)	24.08±0.51	22.92±0.69	0.205	21.25±1.84	22.43±0.62	0.556
ALT (U/L)	53.63±6.26	54.05±6.52	0.964	80.93±11.54	113.45±17.07	0.146
AST (U/L)	66.3±4.77	79.23±8.6	0.218	89.77±7.60	129.55±19.65	0.088
BUN (mmol/L)	1.66±0.25	1.62±0.31	0.926	1.36±0.17	1.18±0.18	0.488
HDL-C(mmol/L)	0.95±0.14	1.07±0.06	0.461	1.02±0.08	1.17±0.10	0.258
LDL-C (mmol/L)	1.45±0.08	1.41±0.08	0.736	1.66±0.10	1.63±0.07	0.839
TCHO (mmol/L)	2.53±0.18	2.66±0.1	0.546	2.77±0.13	2.82±0.15	0.789
TG (mmol/L)	0.44±0.04	0.54±0.06	0.211	0.59±0.05	0.59±0.05	1.000
TP (g/L)	36.57±1.83	34.95±1.37	0.496	37.93±1.72	40.28±1.67	0.350

Note: GLU, glucose; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TCHO, total cholesterol; TG, triglyceride; TP, total protein.

Table S4. Effects of phage cocktail on the blood routine indices of piglets

Indexes	Day 11			Day 21		
	CON	Phage	*P*-value	CON	Phage	*P*-value
WBC (10^9/L)	18.39±3.24	16.07±0.81	0.514	24.05±2.94	22.67±0.95	0.672
Neu (10^9/L)	5.57±1.20	5.80±1.14	0.893	4.89±0.86	5.72±0.72	0.477
Lym (10^9/L)	11.93±3.41	9.32±1.22	0.486	16.73±2.26	15.12±0.91	0.523
Mon (10^9/L)	0.73±0.12	0.82±0.08	0.569	2.09±0.46	1.53±0.05	0.280
Eos (10^9/L)	0.11±0.01	0.10±0.02	0.538	0.25±0.06	0.17±0.04	0.301
Bas (10^9/L)	0.05±0.01	0.04±0.01	0.591	0.09±0.02^a	0.14±0.01^b	0.037
Neu (%)	33.63±5.89	36.08±6.63	0.788	20.52±3.38	25.15±2.85	0.319
Lym (%)	60.88±6.69	57.97±6.88	0.768	70.03±3.98	66.73±2.97	0.522
Mon (%)	4.53±0.84	5.08±0.49	0.583	8.10±1.49	6.80±0.30	0.412
Eos (%)	0.70±0.14	0.62±0.16	0.700	0.97±0.25	0.73±0.15	0.438
Bas (%)	0.25±0.04	0.25±0.04	1.000	0.33±0.05^a	0.58±0.08^b	0.027
RBC (10^{12}/L)	6.15±0.26	5.90±0.44	0.635	5.98±0.26	6.07±0.28	0.821
HGB (G/L)	114.67±6.08	104.17±3.33	0.161	105.67±1.74	104.17±1.11	0.485
HCT (%)	33.8±1.81	30.47±0.92	0.132	32.88±0.68	31.43±0.37	0.091
MCV (fL)	54.93±1.95	52.33±2.08	0.382	55.28±1.52	52.28±1.78	0.229
MCH (pg)	18.65±0.79	17.90±0.74	0.504	17.83±0.71	17.32±0.64	0.603
MCHC (g/L)	339.5±3.37	341.83±1.82	0.560	322.17±4.98	331.17±2.07	0.126
RDW-CV (%)	21.75±0.89	22.27±0.92	0.695	20.83±0.53	21.72±1.02	0.462
RDW-SD (fL)	42.62±2.13	41.58±0.83	0.666	40.75±1.33	39.83±0.99	0.593
PLT (10^9/L)	341.83±44.23	444.33±64.81	0.221	468.33±73.00	483.83±29.24	0.848
MPV (fL)	9.27±0.37	7.63±1.42	0.292	8.67±0.19	8.50±0.23	0.592
PDW (%)	15.35±0.19	15.15±0.12	0.402	15.65±0.11	15.4±0.16	0.228
PCT (%)	0.32±0.04	0.41±0.06	0.227	0.40±0.06	0.41±0.03	0.915

Note: WBC, white blood cells; Neu, neutrophils; Lym, lymphocytes; Mon, monocytes; Eos, Eosinophils; Bas, Basophils; RBC, red blood cells; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW-CV, red blood cell distribution width variation coefficient; RDW-SD, red blood cell distribution width standard deviation; PLT, platelet count; MPV, mean platelet volume; PDW, platelet distribution width; PCT, platelet-crit.

Note: Different superscript letters in the same row indicate significant differences between groups ($P < 0.05$).

Table S5. Effects of phage cocktail on the relative weight of organs in piglets

Organs (%)	CON	Phage	*P*-value
Heart	0.56±0.02	0.59±0.02	0.382
Liver	2.93±0.13	3.01±0.15	0.699
Spleen	0.28±0.02	0.24±0.01	0.136
Pancreas	0.25±0.02[a]	0.20±0.12[b]	0.050
Kidney	0.59±0.03	0.57±0.01	0.546

Note: Different superscript letters in the same row indicate significant differences between groups ($P < 0.05$).

Table S6. Effects of phage cocktail on the relative weight and length of different intestinal segments of piglets

Segment	Indexes	CON	Phage	*P*-value
Jejunum	Relative length (cm/kg)	63.49±2.46	68.45±1.43	0.103
	Relative total weight (%)	4.26±0.33	4.16±0.22	0.803
	Relative net weight (%)	3.55±0.23	3.56±0.17	0.983
Ileum	Relative length (cm/kg)	1.27±0.16	1.72±0.15	0.071
	Relative total weight (%)	0.11±0.02	0.14±0.01	0.189
	Relative net weight (%)	0.09±0.01[a]	0.14±0.01[b]	0.024
Cecum	Relative total weight (%)	0.46±0.10	0.62±0.09	0.271
	Relative net weight (%)	0.21±0.01	0.22±0.01	0.58
Colon	Relative length (cm/kg)	10.07±0.92	9.95±0.83	0.922
	Relative total weight (%)	2.61±0.23	2.35±0.17	0.388

Note: Different superscript letters in the same row indicate significant differences between groups ($P < 0.05$).

Table S7. Effects of phage cocktail on the digestive enzymes' activity of jejunal digesta

Digestive enzyme (*U*/mgprot)	CON	Phage	*P*-value
Lipase	0.17±0.04	0.12±0.02	0.313
Trypsin	6643.52±1655.35	4355.24±1389.83	0.313
Amylase	13.68±6.69	10.46±2.41	0.660

Table S8. Effects of phage cocktail on the intestinal morphology of piglets

Indexes	CON	Phage	*P*-value
Jejunum villus height (μm)	490.73±94.31	443.95±32.13	0.649
Jejunum crypt depth (μm)	241.98±16.59	241.40±15.39	0.980
villus height/crypt depth	2.10±0.46	1.85±0.13	0.608

Table S9. Effects of phage cocktail on the α diversity of fecal microbiota of piglets

Indexes	Day 11			Day 21		
	CON	Phage	*P*-value	CON	Phage	*P*-value
Observed	2158.83±187.43	1954.67±108.35	0.368	1975.17±87.22	1780.50±190.35	0.374
Chao1	3023.83±214.83	2680.03±134.98	0.205	2799.16±145.53	2524.54±250.00	0.365
ACE	3056.70±226.76	2748.87±137.03	0.272	2842.13±132.76	2545.82±259.44	0.333
Shannon	5.32±0.12	5.25±0.12	0.680	5.18±0.08	5.09±0.17	0.667
Simpson	0.98±0.005	0.98±0.003	0.831	0.98±0.003	0.97±0.005	0.511