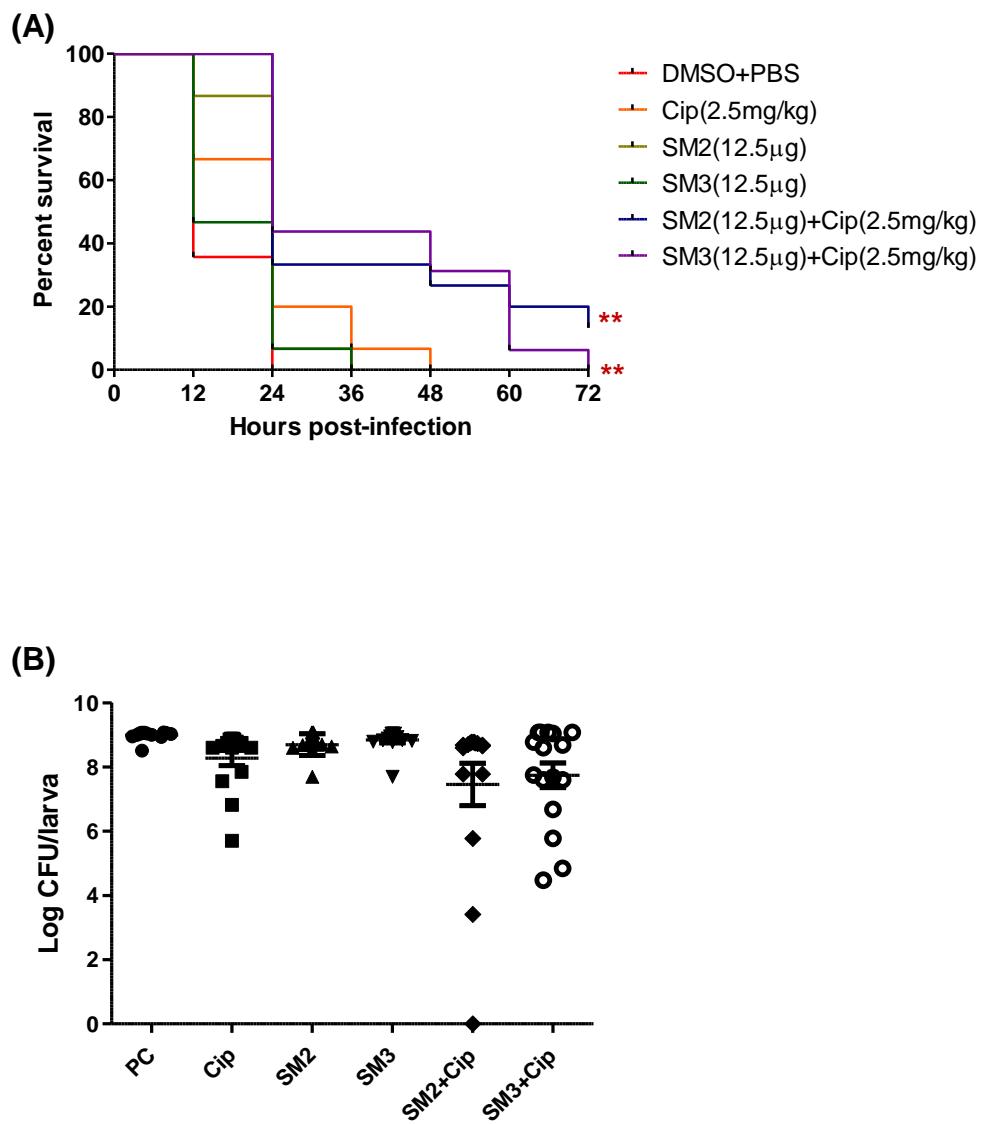
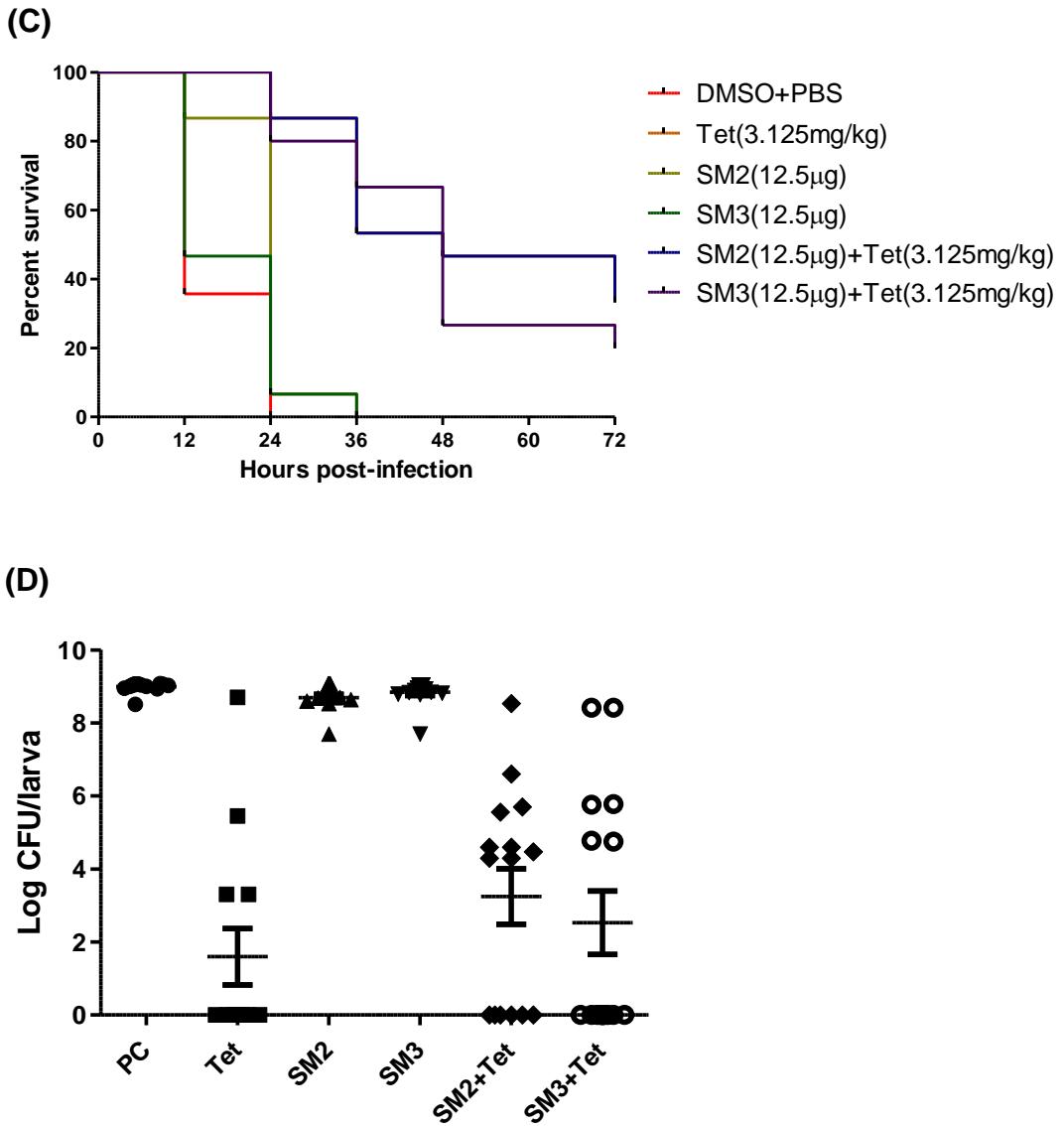


**Fig. S1**



**Fig. S1**

**Fig. S1: A & C)** Survival curve of wax moth larvae treated with ciprofloxacin (**A**) or tetracycline (**C**) alone or in combination with SMs. Larvae (n=15 larva/group) were infected with  $6.4 \times 10^4$  CFU of Rif<sup>r</sup> APEC O78 and then treated with ciprofloxacin (2.5 mg/kg) or tetracycline (1.5625 mg/kg) and combination of ciprofloxacin and SMs (2.5 mg/kg+12.5  $\mu$ g) or combination of tetracycline and SMs (1.5625 mg/kg+12.5  $\mu$ g). **B & D)** APEC load inside wax moth larvae treated with ciprofloxacin (**B**) or tetracycline (**D**) alone or in combination with SMs. PC- infected and buffer mix (DMSO+PBS) treated larvae, \*\*P<0.01.

**Table S1.** MIC and MBC of antibiotics against APEC O78 in M63 media.

Antibiotics	MIC ( $\mu\text{g/mL}$ )	MBC ( $\mu\text{g/mL}$ )
Ciprofloxacin HCL	0.125	1
Colistin sulfate	2	2
Tetracycline HCL	16	128

**Table S2.** MIC and MBC of colistin against APEC O1 and O2 in M63 media.

	APEC O1	APEC O2
MIC ( $\mu\text{g/mL}$ )	4	4
MBC ( $\mu\text{g/mL}$ )	4	4

**Table S3.** Optimization of antibiotics dose for synergy testing in wax moth larva model.

Antibiotic	Dose (mg/kg)	Survival (%)
Colistin	5	100
	2.5	100
	1.25	90
	0.625	70
	0.3125 <sup>†</sup>	20
	0.15625	0
Ciprofloxacin	20	100
	10	80
	5	80
	2.5 <sup>†</sup>	20
	1.25	0
	0.625	0
Tetracycline	50	100
	25	100
	12.5	100
	6.25	90
	3.125 <sup>†</sup>	60
	1.5625	0

<sup>†</sup>dose that provide minimal protection to the larva against APEC O78 infection was selected for synergy testing.

**Table S4.** Primers used in this study.

<b>Primer</b>	<b>Sequence (5' to 3')</b>
PmrC_F	CATCAACGGCGAATGCTATG
PmrC_R	CTGCCGATGGTGTGTAAGA
PmrH_F	CATGCCGTCGGTACGTATTA
PmrH_R	TTACAATCAGGCCACCTTCC
PmrA_F	CCTGCTACGACGCCATAATAA
PmrA_R	CTCTTCACCGCTCATCCATAC
PmrB_F	TCAGCCTGACGCTATTATCTG
PmrB_R	GAATGGCAATGGCGTTAAG
GAPDH_F	CGGTACCGTTGAAGTGAAAGA
GAPDH_R	ACTTCGTCCCATTTCAGGTTAG

**Table S5.** Fractional inhibitory concentration (FIC) indices of SMs when tested with antibiotics against APEC O78.

<b>Fractional inhibitory concentration (FIC) index</b>			
	<b>Colistin</b>	<b>Tetracycline</b>	<b>Ciprofloxacin</b>
SM1	0.9 <sup>I</sup>	1 <sup>I</sup>	2 <sup>I</sup>
SM2	0.2 <sup>S</sup>	0.5 <sup>S</sup>	0.7 <sup>I</sup>
SM3	0.2 <sup>S</sup>	0.2 <sup>S</sup>	1.1 <sup>I</sup>
SM4	0.2 <sup>S</sup>	2 <sup>I</sup>	0.2 <sup>S</sup>
SM5	0.2 <sup>S</sup>	0.5 <sup>S</sup>	0.5 <sup>S</sup>
SM6	0.2 <sup>S</sup>	1.2 <sup>I</sup>	0.9 <sup>I</sup>
SM7	0.2 <sup>S</sup>	0.2 <sup>S</sup>	0.7 <sup>I</sup>
SM8	0.5 <sup>S</sup>	2 <sup>I</sup>	1.2 <sup>I</sup>
SM9	0.2 <sup>S</sup>	0.8 <sup>I</sup>	0.9 <sup>I</sup>
SM10	0.8 <sup>I</sup>	2 <sup>I</sup>	2 <sup>I</sup>
SM11	0.2 <sup>S</sup>	0.6 <sup>I</sup>	0.5 <sup>S</sup>

<sup>S</sup>synergy; <sup>I</sup>indifferent

**Table S6.** ID, molecular weight, and molecular name of the SMs.

<b>ID</b>	<b>Mol Name</b>	<b>Mol Weight</b>
38183621	1-[2-methoxy-4-({[2-(2-naphthyl)ethyl]amino}methyl)phenoxy]-3-(1-pyrrolidinyl)-2-propanol	434.6
44636789	1-[2-methoxy-4-({[2-(4-methylphenyl)ethyl]amino}methyl)phenoxy]-3-(1-pyrrolidinyl)-2-propanol	398.5

**Table S7.** Synonymous mutations observed in Col<sup>R</sup> APEC isolates.

<b>Product (CP004009 (CDS))</b>	<b>Type of mutations</b>
hypothetical proteins [AGC85973.1, AGC85995.1, AGC85542.1, AGC85231.1, AGC85972.1, AGC85975.1, AGC85991.1]	SNVs
putative transposases [AGC87419.1]	SNVs
phage replication protein O [AGC84960.1]	SNVs
antitermination protein Q from phage origin [AGC86222.1]	SNVs
Increased serum survival (Iss) [AGC85979.1]	SNV
Rz endopeptidase from lambda prophage DLP12 [AGC86226.1]	SNVs
lambda prophage DLP12 Bor-like protein [AGC86227.1]	SNVs
phage repressor protein [AGC85996.1]	SNVs
terminase large subunit [AGC87037.1]	SNVs
restriction alleviation protein [AGC86220.1]	SNV
bacteriophage lysis protein [AGC85980.1]	SNV
electron transport complex protein RnfC [AGC87121.1]	SNV