Supplementary materials

Table S1. Studies on combination between fosfomycin and different antibiotics. CB: checkerboard assay; TK: time-kill assay; ET: E-test.

Strain	Year and Country	Author	Antibiotic	Number of isolates	Known Resistance Mechanisms or Determinants (%)	FOS-resistant (%)	Other drug-resistant (%)	In Vitro (Methods)/in Vivo (animal and Site of Infection)	Synergistic effect (%)	Additive Effect (%)	Indifferent Effect (%)	Antagonistic Effect (%)	FOS Susceptibility Restoration (%)	Other drug Susceptibility Restoration (%)	Comments	Reference
H. pylori	2005, Austria	Blacky	Metronidazole	24	-	0%	33%	in vitro (CB)	0%	21%	100%	4%	-	-	-	[1]
Intestinal bacteria (not specified)	1984, Sweden	Nord	Metronidazole	-	-	-	-	in vivo (rats, intra-abdominal infection)	-	-	-	-	-	-	Animal treated with MTZ + FOS showed a significantly decrease mortality and increase cure rates. Mortality with MTZ alone was 40%, FOS alone 33%, MTZ + FOS 7%.	[2]
N. gonorrhoeae	2015, The Netherlands	Wind	Spectinomycin	4	-	-	-	in vitro (ET)	-	-	-	-	-	-	Only 1/4 isolate showed a FIC < 1. If the FICI was < 1.0 in at least 3 of the 4 tested isolates for a specific combination, that combination was re-tested with microdilution method. The combination FOS + SCM none are promising candidates for gonorrhoea dual therapy.	[3]
A. baumannii	2011, USA	Santimaleeworagun	Sulbactam	8	OXA-23 (100%)	100 %	75%	in vitro (CB, TK)	75%	0%	25%	0%	-	-	-	[4]
S. aureus	1978, Spain	Olay	Lincomycin	37	-	-	-	in vitro (CB)	81%	19%	0%	0%	-	-	-	[5]
P. aeruginosa (n=1) and other (not specified)	1977, Spain	Daza	Nitroxoline	8	-	100 %	-	in vitro (CB in agar)	12%	0%	88%	0%	-	-	-	[6]
S. aureus	2008, France	Duez	Dalfopristin-Quinupristin	6	MRSA (50%)	0%	67%	in vitro (CB)	100%	0%	0%	0%	-	-	-	[7]
S. aureus, S. epidermi	2001, Austria	Grif	Dalfopristin-Quinupristin	6	MRSA (17%), GISA (17%)	-	17%	in vitro (CB, TK)	100%	0%	0%	0%	-	-	-	[8]

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S. aureus	2012, Taiwan	Tang	Fusidic acid	8	MRSA (100%)	6%	12%	in vitro (TK)	100%	0%	0%	0%	-	-	-	[9]
S. aureus	2010, China	Yu	Fusidic acid	196	MRSA (100%)	100 %	100 %	in vitro (CB)	88%	12%	0%	0%	100%	100%	-	[10]
S. aureus	1994, France	Drugeon	Fusidic acid	35	MRSA (67%)	0%	100 %	in vitro (double diluition method)	0%	0%	100%	0%	-	-	Synergism: decrease of at least 16% after 6 h in the AUC of survivors and at least a 100-fold increase in killing after 24 h. Additive/indifferent: reduced by less than 10% after 6 h in the AUC of survivors and increase in killing was less than ten-fold after 24 h. Antagonism: increase of more than 16% in the number of survivors after 6 h and a 100-fold increase in viable bacteria after 24 h.	[11]
Enterobacterales	1977, Spain	Daza	Chloramphenicol	100	-	100 (100 %)	-	in vitro (CB)	0%	-	100%	0%	-	-	Authors considered synergistic effect when MIC was at least fourfold lower over initial MIC.	[6]
E. coli	1978, Spain	Olay	Chloramphenicol	90	-	-	-	in vitro (CB)	37,8%	Partial Synergy: 47,8%	14,4%	0%	-	-	Authors considered **Synergistic effect** when MIC of both antimicrobials was at least fourfold lower over initial MIC; **partial synergy** when MIC of one antimicrobials was at least fourfold lower and MIC of the other one 2 times lower over initial MIC; **Indifferent effect** when MIC of both antimicrobials was 2 times lower; **antagonism** when MIC of both increased 4 times over initial MIC.	[5]
Klebsiella spp.	1978, Spain	Olay	Chloramphenicol	56	-	-	-	in vitro (CB)	35,7%	Partial Synergy: 41,1%	23,2%	0%	-	-	Authors considered **Synergistic effect** when MIC of both antimicrobials was at least fourfold lower over initial MIC; **partial synergy** when MIC of one antimicrobials was at least fourfold lower and MIC of the other one 2 times lower over initial MIC; **Indifferent effect** when MIC of both antimicrobials was 2 times lower; **antagonism** when MIC of both increased 4 times over initial MIC.	[5]
Proteus spp. *(Indole +)*	1978, Spain	Olay	Chloramphenicol	34	-	-	-	in vitro (CB)	55,9%	Partial Synergy: 20,6%	23,5%	0%	-	-	Authors considered **Synergistic effect** when MIC of both antimicrobials was at least fourfold lower over initial MIC; **partial synergy** when MIC of one antimicrobials was at least fourfold lower and MIC of the other one 2 times lower over initial MIC; **Indifferent effect** when MIC of both antimicrobials was 2 times lower; **antagonism** when MIC of both increased 4 times over initial MIC.	[5]
P. aerugino	1978, Spain	Olay	Chloramphenicol	19	-	-	-	in vitro (CB)	52,6%	Partial Synergy:	10,5%	0%	-	-	Authors considered **Synergistic effect** when MIC of both antimicrobials was at least fourfold lower over initial MIC; **partial synergy** when MIC of one	[5]

sa										36,9%				antimicrobials was at least fourfold lower and MIC of the other one 2 times lower over initial MIC; **Indifferent effect** when MIC of both antimicrobials was 2 times lower; **antagonism** when MIC of both increased 4 times over initial MIC.	
Salmonella spp.	1978, Spain	Olay	Chloramphenicol	32	-	-	-	in vitro (CB)	28,1%	Partial Synergy: 62,5%	9,4%	0%	-	-	Authors considered **Synergistic effect** when MIC of both antimicrobials was at least fourfold lower over initial MIC; **partial synergy** when MIC of one antimicrobials was at least fourfold lower and MIC of the other one 2 times lower over initial MIC; **Indifferent effect** when MIC of both antimicrobials was 2 times lower; **antagonism** when MIC of both increased 4 times over initial MIC.	[5]
	1978, Spain	Perea	Chloramphenicol	90 (2 TK)	-	10%	27%	in vitro (CB, TK)	CB: 17 (18,9%) / TK: 1 (50%)	CB: 48 (53,3%) / TK: 1 (50%)	CB: 13 (14,4%) / TK: 0%	0%	-	-	CK: 12 strains reported as " Not Evaluable"; Only 2 strains evaluated with TK.	[12]
S. typhi	1977, Spain	Figuero a	Chloramphenicol	16	-	0%	-	in vitro (CB)	14 (87,5%)	2 (12,5%)	0%	0%	-	-	The authors considered synergistic the effect for FICI up to < 1 and additive the effect for FICI = 1. They also evaluated different antibiotic combinations in clinical experience on patients with typhoid fever: FOS + AMP in higher rates of cure then FOS + CAF combination.	[13]
Shighella spp.	1978, Spain	Perea	Chloramphenicol	50	-	54%	56%	in vitro (CB, TK)	CB: 11 (22%) / TK: 1 (50%)	CB: 28 (56%) / TK: 0%	CB: 9 (18%) / TK: 1 (50%)	0%	-	-	CK: 2 strains reported as " Not Evaluable"; Only 2 strains evaluated with TK.	[12]
S. aureus	1978, Spain	Olay	Chloramphenicol	48	-	-	-	in vitro (CB)	21 (43,8%)	Partial Synergy: 18 (37,5%)	9 (18,7%)	0%	-	-	Authors considered **Synergistic effect** when MIC of both antimicrobials was at least fourfold lower over initial MIC; **partial synergy** when MIC of one antimicrobials was at least fourfold lower and MIC of the other one 2 times lower over initial MIC; **Indifferent effect** when MIC of both antimicrobials was 2 times lower; **antagonism** when MIC of both increased 4 times over initial MIC.	[5]
Enterobacterales	1977, Spain	Daza	Nitrofurantoin	100	-	100 (100 %)	-	in vitro (CB)	0%	-	100%	0%	-	-	Authors considered synergistic effect when MIC was at least fourfold lower over initial MIC.	[6]
E. faecium	2012, USA	Descouruez	Nitrofurantoin	32	VRE (100%)	9%	100 %	in vitro (TK)	0%	0%	100%	0%	-	-	The authors considered MIC ≤ 64 mg/L as FOS breakpoint.	[14]
Enterobacterale	2019, USA	Flamm	TMP/SMX	20	7/30 MDR strains (*A. baumannii*, Enterobacterales and	-	-	in vitro (CB)	2 (10%)	6 (30%)	7 (35%)	0%	-	-	Authors considered Partial Sinergy when FICI was between 0.5–1 and Additive effect for FICI = 1. Results for	[15]

s					*P. aeruginosa*) included 2 ESBL and 2 KPC Enterobacterales										5/20 strains (25%) were indeterminate.	
	1977, Spain	Daza	TMP/SMX	100	-	100 (100 %)	-	in vitro (CB)	0%	-	100%	0%	-	-	Authors considered synergistic effect when MIC was at least fourfold lower over initial MIC.	[6]
S. aureus	1985, USA	Alvarez	TMP/SMX	148	MRSA (100%)	-	-	in vitro (Microtiter technique 1:1 ratio)	4 (2,7%)	-	140 (94,6%)	4 (2,7%)	-	-	Authors considered Synergistic effect when MIC of both antimicrobials was 1/4 MIC lower, antagonism when MIC of at least 1 antimicrobial was four times higher and Indifferent all other cases.	[16]

Table S2. Studies on combination between fosfomycin and molecules other than antibiotics. CB: checkerboard assay; TK: time-kill assay.

Strain	Year and Country	Author	Molecule	Number of Isolates	Known Resistance Mechanisms or Determinants (%)	FOS-resistant (%)	In Vitro (Methods)/in Vivo (Animal and Site of Infection)	Synergistic Effect (%)	Additive Effect (%)	Indifferent Effect (%)	Antagonistic Effect (%)	FOS Susceptibility Restoration (%)	Comments	Reference
L. monocytogenes	2020, USA	Zhang	Chlorogenic acid, Caffeic acid	NS		100%	in vitro (bacterial cell growth study)	100%	0%	0%	0%	Chlorogenic acid: 100% (if chlorogenic acid was 3 mg/L)	Reduction in the cell growth equal to 98% with chlorogenic acid and 85,2% with caffeic acid.	[17]
S. aureus, S. enterica subsp. Bukuru, E. coli	2020, Egypt	Abo-Shama	Silver (AgNPs) and zinc oxide (ZnONPs) nanoparticles	3	-	-	in vitro (disk diffusion)	AgNPs: 100% ZnONPs: 100%	0%	0%	0%	-	-	[18]
S. aureus, S. epidermidis	2019, China	She	Auranofin	4	MRSA (75%)	0%	in vitro (CB); in vivo (mouse, cutaneous infection model)	50%	25%	25%	0%	-	AF combined with FOS synergistically inhibited abscess and inflammation formation and reduced the bacterial load for both MSSA and MRSA strains.	[19]
P. aeruginosa	2019, Canada	Domalaon	Dilipid ultrashort cationic lipopeptides	1	-	-	in vitro (CB)	100%	0%	0%	0%	-	-	[20]
P. aeruginosa	2018, Canada	Yang	Tobramycin-efflux pump inhibitor conjugates	1	-	0%	in vitro (CB)	100%	0%	0%	0%	100%	-	[21]
P. aeruginosa	2017, Canada	Lyu	Amphiphilic lysine-tobramycin conjugates	1	-	0%	in vitro (CB)	100%	0%	0%	0%	100%	-	[22]
S. aureus	2017, Iran	Akbari-Ayezloy	β-chloro-L-alanine	11	MRSA (100%)	9%	in vitro (tube diluition method)	100%	0%	0%	0%	-	The authors used the ANOVA analysis to evaluate the effectiveness of the combination. The combination reduces the formation of biofilm.	[23]
E. faecalis	2015, France	Breidenstein	Plectasin NZ2114	1	VanA (100%)	-	in vitro (disk diffusion, CB, TK)	0%	0%	100%	0%	-	The authors stated there was not synergistic effect, without specifying if the effect was additive, indifferent or antagonistic.	[24]
Enterococcus spp., S. aureus	2008, Japan	Sakagami	2 Quinolone derivatives: A and B	14	MRSA (64%) VRE (36%)	-	in vitro (doubling dilution method)	A: 100% B: 64% (MRSA)	A: 0% B: 36% (VRE)	A: 0% B: 0%	A: 0% B: 0%	-	Compound A: 8-[3-[(ethylamino) methyl] -1-pyrrodinyl] -7-fluoro-9,1-[(Nmethylimino) methano] -5-oxo-5H-thiazolo [3, 2-a] quinolone-4-carboxylic acid; Compound B: 7-fluoro-8-morpholino-9, 1-[(N-methylimino)methano] -5-oxo -5H- thiazolo [3, 2-a]	[25]

													quinolone-4-carboxylic acid.	
E. coli	2003, Italy	Marchese	N-acetylcysteine	4	-	-	in vitro (formation or disruption of biofilms)	-	-	-	-	-	FOS plus N-acetylcysteine reduced biofilm; the most effective combination was that obtained using FOS at 2000 mg/l and NAC at 2 mg/ml.	[26]
S. aureus	1998, Japan	Sakagami	Sophoraflavanone G	6	MRSA (100%)	-	in vitro (doubling dilution method)	100%	0%	0%	0%	-	-	[27]
P. vulgaris, S. gallinarum	1988, USA	Dulaney	Arenaemycin	2	-	0%	in vitro (doubling dilution method)	100%	0%	0%	0%	-	-	[28]

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