Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci **August 2021; 7(2):178-185**

RESEARCH ARTICLE **DOI:** 10.19127/mbsjohs.817255

In Vitro Interactions of Antibiotics with Drugs Used in Chronic Diseases

Esra Erdogan[1(ID)], Selami Gunal[1(ID)]

[1]Inonu University Faculty of Pharmacy, Department of Pharmaceutical Microbiology, Malatya, Turkey

Received: 03 November 2020, Accepted: 15 April 2021, Published online: 31 August 2021

Abstract

Objective: In this century, with the prolonged life expectancy, chronic diseases have become the most important cause of mortality and morbidity in the world and in our country. Frequent drug-drug interactions have made it necessary to update the doses of drugs in multiple drug use. In our study, we aimed to observe how the drugs that are frequently prescribed by physicians in the treatment of chronic and infectious diseases, together with standard bacteria and fungi strains in *in vitro* environment, change the effects of each other.

Methods: By combining antibiotic discs and drugs that are commonly used in chronic diseases (acetylsalicylic acid, amlodipine, atorvastatin, warfarin, metoprolol and clopidogrel) in *in vitro* environment, we determined the drug interactions (synergy/antagonism) by Kirby Bauer disk diffusion method.

Results: While most of the discs placed on the culture of *Candida albicans* through impregnation of drugs showed potentiation synergism with itraconazole and fluconazole, other microorganisms showed synergistic and sometimes antagonistic interactions with different drugs and antibiotics, whereas some of the drugs did not show any interaction with antibiotic discs.

Conclusion: Due to the strong relationship between advanced age and the number of prescribed drugs and the frequency of possible drug-drug interactions, the elderly people especially are susceptible to this situation. Infections caused by resistant bacteria cause an increase in disease/death rates and treatment costs. With the awareness that the only difference between drug and poison is the dose, all health professionals especially doctors and pharmacists and patients have a responsibility towards the rational use of drugs.

Key words: Antibiotics, chronic diseases, disk diffusion method, drug interactions

Suggested Citation: Erdogan E, Gunal S. *In Vitro* Interactions of Antibiotics with Drugs Used in Chronic Diseases Mid Black Sea J of Health Sci. 2021; 7(2):178-185

Address for correspondence/reprints:
Esra Erdogan

Telephone number: 0(506) 4768040

E-mail: eczesraerdogan@gmail.com

Introduction

The World Health Organization (WHO) estimates the non-contagious diseases (NCDs), including cancer, cardiovascular diseases, stroke, chronic lung diseases and diabetes to be responsible for approximately 70% of deaths worldwide (1). With the increase in life expectancy and the changing burden of diseases, the NCD prevalence and its share in the causes of death are increasing day by day in our country, as in the whole world (2).

The frequency and incidence of chronic diseases increase with old age, and this process requires the use of multiple drugs. Since geriatric patients are particularly sensitive to interactions, possible drug-drug interactions can be seen frequently in those patients. Drug-drug interactions can lead to positive or negative consequences. Unwanted drug-drug interactions ought to be considered as they cause 10-20% of drug reactions that require hospitalization, and this process can be prevented (3).

Elderly patients are at higher risk of infection compared to adults, and the rational use of antibiotics can be lifesaving for them. For proper antibiotic use, correct antibiotic should be administered after correct diagnosis in the most appropriate way, at effective dose, at optimal intervals, and for the appropriate duration. The most common bacterial infections in the elderly are urinary tract infections, pneumonia, skin, and soft tissue infections. Unnecessary antibiotic use may cause drug toxicity, allergic reactions, secondary infections, and antibiotic resistance. Antibiotics, in terms of problems caused by irrational drug use, not only affect the person, but they differ from other drugs by affecting the society, environment, and new generations as well (4).

Considering the fact that our country ranks first among 46 countries in the WHO European Region in terms of antibiotic consumption) and one third of the society is exposed to chronic diseases, it is inevitable that drug-drug interactions will occur as a result of the combined use of antibiotics and drugs that are used for chronic diseases. Drug interaction can be seen as an antagonistic as well as a synergistic interaction (5).

In this study, we aimed to examine the drug interactions in detail using the disk diffusion method by combining microorganisms that frequently cause infectious diseases, the antibiotics kept in *in vitro* environment and drugs used extensively in chronic diseases. By this way, we aimed to reduce the duration and costs of treatment and contribute to the rational drug use by trying to enlighten the drug-drug interactions, which are among the factors determining the effectiveness of the treatment.

Methods

S. aureus ATCC 29213, Methicillin-resistant *S. aureus* (MRSA) ATCC 43300, *E. faecalis* ATCC 29212, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *A. baumannii* ATCC 19606, *K. pneumoniae* ATCC 700603 and *C. albicans* ATCC 10231 strains were provided by Malatya Inonu University Faculty of Pharmaceutical Microbiology laboratory. Amoxicillin-clavulanic acid (AMC 30), Sulbactam-ampicillin (SAM 20), Ciprofloxacin (CIP 5), Penicillin (P 10), Clarithromycin (CLR 15), Trimethoprim-sulfamethoxazole (SXT 25), Meropenem (MEM 10), Colistin (CT 10), Tigecycline (TGC 15), Vancomycin (VA 30), Levofloxacin (LEV 5), Tetracycline (TE 30), Ceftriaxone (CRO 30), Cefazolin (CZ 30), Cefuroxime (CXM 30), Teicoplanin (TEC 30), Linezolid (LNZ 30), Gentamicin (CN 10), Amikacin (AK 30), Amphotericin B (AMB 100), Fluconazole (FLU 25) and Itraconazole (ITR 10) discs were used in this study.

Mueller Hinton Agar (MHA) medium (Merck, Germany), Mueller Hinton Broth (MHB) medium (Merck, Almanya), Sabouraud Dextrose Agar medium (Merck, Germany) and Tryptic Soy Agar medium (Merck, Germany) were prepared as described and were sterilized at 121°C for 15 minutes in an autoclave and, thus, the petri dishes to be used in our study were prepared for the cultivation purposes.

In this study, acetylsalicylic acid (aspirin 100mg tablet/bayer), warfarin (coumadin 5mg tablet/zentiva), amlodipine (vazkor 5mg tablet/deva), atorvastatin (ator 10mg tablet/sanovel), metoprolol (beloc zok 25mg tablet/astrazeneca), clopidogrel (plavix 75mg tablet/sanofi), as well as the dual combinations of all above-mentioned drugs, were powdered using porcelain mortar, dissolved in distilled water and were made to be absorbed into sterile blank paper discs. We dissolved each tablet in distilled water and absorbed the mixture on blank discs. Each of the discs, which we prepared by absorbing the drug or dual combinations of drugs, contained different concentrations of the drugs (Acetylsalicylic acid 1000µg, warfarin 50µg, amlodipine 50µg, atorvastatin 100µg, metoprolol

250µg and clopidogrel 750µg were absorbed on paper discs).

The standard microorganisms were incubated in liquid medium (Mueller Hinton Broth) for 2 hours at 37°C. A standard turbidity was prepared by adjusting the medium according to 0.5 McFarland standard (1.5×10^8 microorganisms/ml). This suspension was cultivated using a sterile swab with the spreading technique in petri dishes containing MHA prepared beforehand.

Each of the bacteria was placed on the agar surface with the help of sterile forceps, using all the standard antibiotic discs, in such a way that the disc which impregnated the relevant drug was in the middle of the petri dish. We placed ready-made antibiotic discs around the discs that were prepared by absorbing drugs into sterile blank paper discs.

Then, the media were incubated for 18-24 hours at 35°C in the incubator and the resulting inhibition zones were evaluated (6-8)

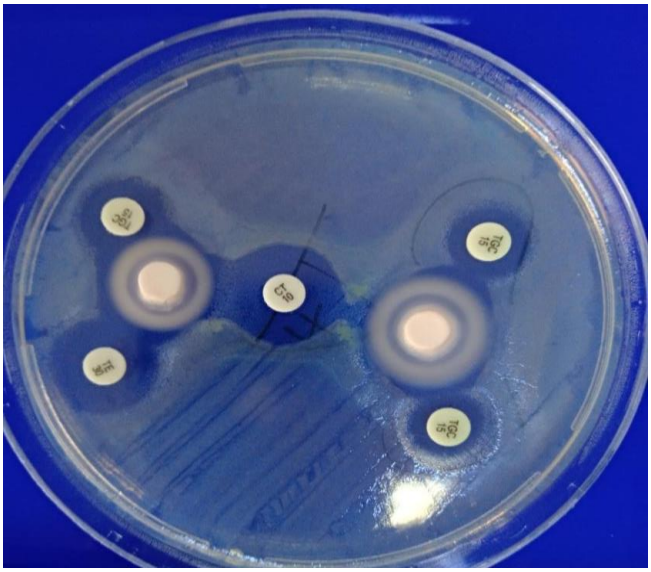

Figure 1. Synergism between TGC and Plavix in *P. aeruginosa* cultivated plate

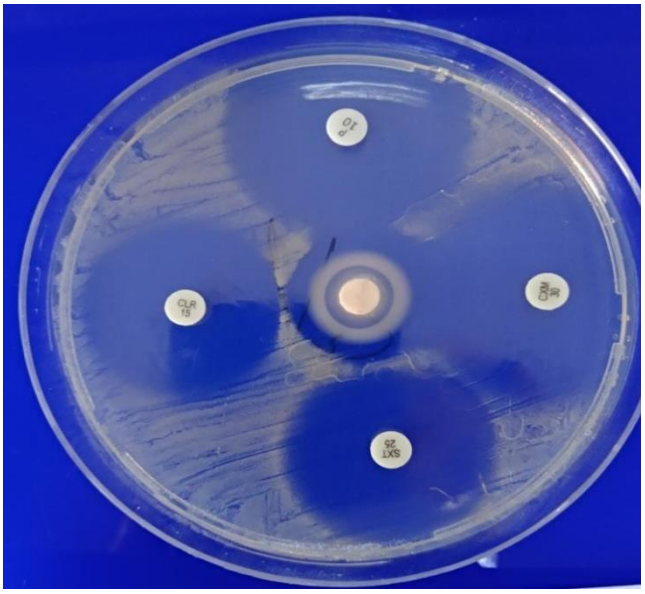

Figure 2. Antagonism between CLR and Plavix in *S. aureus* cultivated plate

Results

In our study, we used acetylsalicylic acid, warfarin, amlodipine, atorvastatin, metoprolol and clopidogrel, which are drugs commonly used in chronic diseases. We impregnated these drugs one by one and in combinations of two on our empty discs. We placed the discs on the plates we prepared and recorded the interactions seen as antagonism and synergism. In Figure 1 there is synergism between TGC antibiotic disc and Plavix disk (which prepared by us) in P. aeruginosa cultivated plate. In Figure 2 there is antagonism between CLR antibiotic disk and Plavix disk in S. aureus cultivated plate.

The highest interaction was observed with Plavix. All the interactions that took place were gathered in Table 1. The photos of some interactions are as follows;

Table 1. All interactions that took place as antagonism and synergism.

	S. aureus	*E. faecalis*	*E. coli*	*P. eruginosa*	*C. albicans*	*A. baumannii*	*K. pneumoniae*	MRSA
aspirin	TEC, TGC				FLU, ITR			
vazkor			CXM, TGC, CLR		FLU, ITR		LEV	
ator					FLU, ITR			
beloc			CT			CLR		
coumadin		CLR			FLU, ITR			
plavix	TEC, TGC, CIP, CLR	MEM, VA, TGC,P, CLR	CXM, TGC	TGC, AK	FLU, ITR	AMC, TGC, CLR	TE, CT, LEV	TEC, CXM
vazkor+aspirin				TGC	FLU, ITR	TE, CT, CLR	TE, CZ	
ator+aspirin				LEV	FLU, ITR			SXT
beloc+aspirin			CZ		FLU, ITR	TGC		
coumadin+aspirin				CT	FLU, ITR		CT	CIP
plavix+aspirin	CXM	TGC, P, SXT		CT	FLU, ITR	CT, AK, TGC, CLR		
ator+vazkor	AMC		CRO, LEV, AMC		FLU, ITR			LNZ, SXT, MEM
beloc+vazkor				CZ	FLU, ITR	TGC, LEV, TE	TE, CRO	
coumadin+vazkor		CN			FLU, ITR			
plavix+vazkor	MEM, AMC	LNZ, AMC		CZ	FLU, ITR		CT	CIP, MEM
beloc+ator	AMC			LEV	FLU, ITR			
coumadin+ator	AMC	AMC			FLU, ITR			
plavix+ator	AMC	AMC, LNZ			FLU, ITR			
coumadin+beloc	CIP, CN	LNZ, SAM			FLU, ITR			LNZ
plavix+beloc			CXM, TGC	CZ	FLU, ITR, AMB			CXM
plavix+coumadin	AMC, LNZ	AMC, SXT			FLU, ITR			

Note: Among the antibiotic symbols used in the table, black symbols show synergistic and red symbols show antagonistic interactions.

Discussion

Irrational drug use is a common public health problem. According to WHO data, it is known that more than 50% of all drugs are improperly prescribed, supplied or sold worldwide. Furthermore, 50% of the patients do not use their medication correctly. Also, unfortunately, one third of the world population is unable to have access to essential drugs. Due to the increase in the elderly population worldwide, the use of multiple drugs in the treatment of chronic diseases has become an important economic problem both in terms of public health and an increase in health costs (9).

As people get older, the reactions and transmissions occurring in the brain and the body suffer from malfunctions due to the loss of function of the related tissues. As a result of human aging, the function of homeostasis mechanism, which is one of the most important factors affecting the pharmacokinetics of drugs and the progression of diseases, decreases and the sensitivity of the receptors towards related chemicals changes. It is the duty of clinicians to know how drug-drug interactions occur and how to manage these interactions (10).

The search for combinations of non-antibiotic drugs with antimicrobial agents currently in clinical use has recently regained interest and is a promising approach with many advantages. Information regarding the pharmacological properties (both safety and pharmacokinetics) of non-antibiotic drugs that

are approved by the Food and Drug Administration (FDA) is widely available in pre-clinical and clinical studies. Therefore, the time loss and economic costs associated with repositioning these drugs for other therapeutic applications such as the treatment of bacterial and fungal infections are expected to be minimized (11,12).

In such a time when new antimicrobial drugs are becoming increasingly difficult to be found, it is critical to understand the antimicrobial effects of non-antibiotic drugs and their potential clinical consequences. Antipyretic drugs in particular have been known to have direct and indirect antimicrobial effects for more than 30 years. Among these drugs, studies on the most commonly used acetylsalicylic acid (ASA) are quite abundant (13).

In our study, while Aspirin often showed antibacterial activity alone, it interacted synergistically with the antibiotic discs containing teicoplanin and tigecycline in the plates where we cultivated *S. aureus*, whereas it did not show any antifungal effect alone in the plate where we cultivated *C. albicans*. It showed potentiation synergism on *C. albicans* which are resistant to fluconazole and itraconazole. In other words, while there were no effects of individual drugs alone, they started to show antifungal effect when they came together.

Again, in our study on amlodipine, a widely used Ca channel blocker, it was found that the drug alone did not show any antimicrobial activity. However, when we placed the discs that we impregnated with Vazkor on the plates where we had cultivated *E. coli*, a synergistic interaction occurred with CXM, TGC and CLR. Vazkor showed potentiation synergism with FLU and ITR in *C. albicans* cultivated plates. LEV and amlodipine interacted synergistically in *K. pneumoniae* cultivated plates.

In our study on atorvastatin, which is frequently used as an antihyperlipidemic, we observed that Ator did not have any antimicrobial activity alone, but it created a potentiation synergism with FLU and ITR on *C. albicans* cultivations.

Another drug that we used was Metoprolol, which is commonly used as a β1-adrenergic receptor blocker. It did not show antibacterial and antifungal activity alone in different samples where we applied disk diffusion method. The discs that we impregnated with Beloc created synergism with CT in the *E. coli* cultivated plates and with CLR in the *A. baumannii* cultivated plates.

Warfarin, an anticoagulant drug, stands out with its narrow therapeutic range. It is used with INR follow-up. In our study, coumadin impregnated discs showed synergism with CLR in *E. faecalis* cultivated plates and with FLU and ITR on *C. albicans* cultivated plates.

Among the 7 drugs we used, Plavix with clopidogrel active ingredient showed the most interaction. Plavix showed synergistic interaction with TEC and TGC in *S. aureus* cultivated media, with MEM, VA, TGC and P in *E. faecalis* cultivated plates, with CXM and TGC in *E. coli* cultivated media, with TGC in *P. aeruginosa* cultivated plates, with FLU and ITR in *C. albicans* cultivated plates, with AMC and TGC in *A. baumannii* cultivated media, with TE and CT in media cultivated with *K. pneumoniae* and with TEC and CXM in our *S. aureus* MRSA cultivated plates. And it showed antagonistic interaction with CIP and CLR in our *S. aureus* cultivated plates, with CLR in *E. faecalis* cultivated media, with AK in *P. aeruginosa* cultivated plates, with CLR in *A. baumannii* cultivated media, and with LEV in *K. pneumoniae* cultivated media.

Aspirin has been shown to induce efflux-mediated resistance against quinolones in some *E. coli* strains (14). High concentrations of salicylicacid have been shown to reduce the production of flagellin, a virulence factor in *E. coli* which is responsible for motility, and alter the expression of more than 144 genes (15).

Rosner showed that aspirin and salicylic acid reduce the susceptibility of *E. coli* to ampicillin, cephalosporin, chloramphenicol, fluoroquinolones, nalidixic acid and tetracycline antibiotics (16). Aumercier et al. showed that the sensitivity of *E. coli* to aminoglycosides increased with salicylate (17).

P. aeruginosa is an opportunistic and hospital-acquired cause of infection, especially in immuno-compromised patients. It is associated with a high rate of antibiotic resistance and biofilm formation. In studies on *P. aeruginosa*, it has been shown that the use of SAL and ASA alters the expression of more than 331 genes, reduces the production of hemolysin, elastase, protease and pyocyanin by approximately 55%, and effectively inhibits quorum sensing, which is an important virulence factor, motility, biofilm, and toxin formation (18,19).

Bazyleu and Kumar showed that salicylate regulates the expression of porins, and efflux pumps and increases the sensitivity of *A. baumannii* to ceftriaxone, ciprofloxacin, gentamicin and imipenem antibiotics by comparing MIC values (20).

In a study conducted by Domenico et al. on *K. pneumoniae*, it was found that salicylate decreased the sensitivity of *K. pneumoniae* to aztreonam, cefazolin, cefoperazone, ceftizoxime, clindamycin, doxycycline, norfloxacin, and trimethoprim-sulfamethoxazole antibiotics, whereas it increased the sensitivity of *K. pneumoniae* to amikacin, gentamicin, and tobramycin (21).

Chan et al. showed that aspirin alone is not as effective as commonly used antibiotics. However, when it is used along with cefuroxime and chloramphenicol, it can resist more effectively against MRSA by having a synergistic interaction (22). In their study on *S. aureus* in Australia, Gustafson et al. showed that salicylate and acetylsalicylate increased the resistance of ciprofloxacin, a fluoroquinolone used in the treatment of staphylococcal infections. According to a study, *E. coli, K. pneumoniae, P. aeruginosa* and *P. cepacia* are some of the bacteria that cause increased resistance to quinolones in the presence of disalicylate (23).

In different studies conducted on *Candida* species, the use of aspirin alone or combined with amphotericin B and azoles in treatment has been shown to increase the activity against biofilm-related infections by showing antibiofilm properties (4, 24, 25).

In a study conducted on calcium channel blockers called cinnarizine, verapamil, nifedipine, nimodipine against C. *albicans*, it was found that the use of drugs alone and combined with ketoconazole showed antifungal activity at high concentrations and the effect of verapamil alone was detected to be higher than the others (26).

In their study, Liu et al. investigated the combined use of calcium channel blockers and fluconazole on *Candida*. They also showed that the combined use of amlodipine with fluconazole caused a synergistic interaction against resistant *C. albicans* by causing downregulation in some genes (27).

In an *in vitro* study conducted by Hu et al. on *A. baumannii*, one of the common agents of nosocomial infections, it was reported that the combined treatment of amlodipine and imipenem showed synergistic antimicrobial activity against 64 strains of *Acinetobacter* by inhibiting some genes belonging to efflux pumps (28).

In another study conducted on *A. baumannii*, Li et al. showed that the combined use of imipenem and amlodipine, which is frequently preferred in treatment, increased the antibiotic activity of carbepem in 52 strains compared to the effectiveness of the drug alone (29).

Statins have been found to have bacteriostatic activity in *in vitro* studies at doses exceeding normal serum concentration levels during statin treatment against clinically important bacteria such as *S. aureus, E. coli* and *P. aeruginosa* (30).

In their studies on *S. aureus, E. coli, P. aeruginosa* and *C. albicans* in 2008, Kruszewska et al. reported that clopidogrel showed antibacterial activity against *S. aureus* (31).

In a study conducted by Chen et al. in 2020, it was shown that the INR of patient streated in combination with warfarin and azole derivative antifungal agents increased by more than 20% as compared to patients using warfarin alone. According to this study, as the inclusion of azole group drugs in the treatment of patients undergoing warfarin treatment increases the anticoagulant efficacy of warfarin, the INR values need to be closely monitored in these patients (32).

In their *in vitro* study using six statins, Lima et al. determined that statins show high selectivity for fungal cells as compared to bacteria, and also that some statins when combined with azoles show synergistic interactions. According to this study, statins show antifungal activity *in vitro*, whereas they show anti-inflammatory activity *in vivo* (33).

Conclusion

We may observe many interactions when we use drugs either alone or combined with other drugs. When all these interactions are evaluated, we understand that drug-drug interactions can never be ignored. Our study in particular shows that an important reason for the infection related high mortality and morbidity in more sensitive, comorbid patients who need to use more drugs, patients receiving immunosuppressive therapy etc, may be antagonisms or synergisms that may result from combined use of drugs. It is the duty of all healthcare professionals to prevent possible undesirable drug interactions from occurring. Healthcare professionals should train themselves well on this issue and they should constantly follow up-to-date information. It is desirable to prevent these interactions before they take place. The need for further studies on this issue continues to increase. This research was supported by Inonu University Scientific Research Projects Unit with the Project Number TDK-2018-1376.

Peer-review: Externally peer-reviewed.
Author Contributions: Concept: E.E-S.G. ***Design:*** E.E-S.G. ***Literature Search:*** E.E-S.G. ***Data Collection and Processing:*** E.E-S.G. ***Analysis or Interpretation:*** E.E-S.G. ***Writing:*** E.E-S.G.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: • This research was supported by Inonu University Scientific Research Projects Unit with the Project Number TDK-2018-1376.

References

1. World Health Organization. Major NCDs and their risk factors 2018. https://www.who.int/ncds/introduction/en/ 23 Mart 2019.
2. World Health Organization. Natıonal Household Health Survey in Turkey Prevalence of Noncommunıcable Disease Factors 2017. https://www.who.int/ncds/surveillance/steps/WHO_Turkey_Risk_Factors_A4_TR_19.06.2018.pdf 24 Mart 2019.
3. Snyder BD, Polasek TM, Doogue MP. Drug interactions: principles and practice. Aust Prescr.2012, 35: 85-8.
4. Stepanović S, Vuković D, Ješić M, Ranin L. Influence of acetylsalicylic acid (aspirin) on biofilm production by *Candida* species. J Chemother 2004, 16: 134-8.
5. T.R. Ministry of Health. Yearbook of Health Statistics. Ankara 2016. https://dosyasb.saglik.gov.tr/Eklenti/13183,sy2016turkcepdf.pdf24 Mart 2019.
6. Clinical and Laboratory Standards Institute (CLSI), Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard 13th Edition. CLSI Document, M02Ed13E, 1-56238-834-7 M022018.Clinical and Laboratory Standards Institute 950 West Valley Road, Suite 2500 Wayne, PA 19087 USA.
7. Clinical and Laboratory Standards Institute (CLSI), Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard 11th Edition. CLSI Document, M02Ed13E, 1-56238-834-7M07 2018. Clinical and Laboratory Standards Institute 950 West Valley Road, Suite 2500 Wayne, PA 19087 USA.
8. Clinical and Laboratory Standards Institute (CLSI), Performance Standards for Antifungal Susceptibility Testing of Yeast. 1st ed. CLSI supplement M60.2018. Clinical and Laboratory Standards Institute 950 West Valley Road, Suite 2500 Wayne, PA 19087 USA
9. Beggi B. Rational Drug Use and Polypharmacy Approach in Family Medicine. Antalya Health Practice and Research Center, Family Medicine Clinic. PhD thesis, Antalya: University of Health Sciences, 2018.
10. Koroglu AL. Investigation of drug interactions and dose overconnections in geriatric patient prepaids. Institute of Health Sciences, Department of Clinical Pharmacy. Master Thesis, Istanbul: Istanbul Medipol University, 2018.
11. Miró-Canturri A, Ayerbe-Algaba R, Smani Y. Drug repurposing for the treatment of bacterial and fungal infections. Front Microbiol 2019, 10: 41.
12. Younis W, Thangamani S, MN S. Repurposing non-antimicrobial drugs and clinical molecules to treat bacterial infections. Curr Pharm Des 2015, 21: 4106-11.
13. Zimmermann P, Curtis N. Antimicrobial effects of antipyretics. Antimicrob Agents Chemother 2017, 61: 1-12.
14. Laudy AE, Mrowka A, Krajewska J, Tyski S. The influence of efflux pump inhibitors on the activity of non-antibiotic NSAIDS against gram-negative rods. PloS One 2016, 11: 1-16.
15. Repaske DR, Adler J. Change in intracellular pH of *Escherichia coli* mediates the chemotactic response to certain attractants and repellents. J Bacteriol 1981, 145: 1196-208.
16. Rosner JL. Nonheritable resistance to chloramphenicol and other antibiotics induced by salicylates and other chemotactic repellents in *Escherichia coli* K-12. Proc Natl Acad Sci USA 1985, 82: 8771-4.
17. Aumercier M, Murray DM, Rosner JL. Potentiation of susceptibility to aminoglycosides by salicylate in *Escherichia coli*. Antimicrob Agents Chemother 1990, 34: 786-91.
18. El-Mowafy SA, Abd El Galil KH, El-Messery SM, Shaaban MI. Aspirin is an efficient inhibitor of quorum sensing, virulence and toxins in *Pseudomonas aeruginosa*. Microb pathog 2014, 74: 25-32.

19. Bandara M, Sankaridurg P, Zhu H, Hume E, Willcox M. Effect of salicylic acid on the membrane proteome and virulence of *Pseudomonas aeruginosa*. Invest Ophthalmol Vis Sci 2016, 57: 1213-20.
20. Bazyleu A, Kumar A. Incubation temperature, osmolarity, and salicylate affect the expression of resistance–nodulation–division efflux pumps and outer membrane porins in *Acinetobacter baumannii* ATCC19606T. FEMS Microbiol Lett 2014, 357: 136-43.
21. Domenico P, Hopkins T, Cunha BA. The effect of sodium salicylate on antibiotic susceptibility and synergy in *Klebsiella pneumoniae*. J Antimicrob Chemother 1990, 26: 343-51.
22. Chan EWL, Yee ZY, Raja I, Yap JKY. Synergistic effect of non-steroidal anti-inflammatory drugs (NSAIDs) on antibacterial activity of cefuroxime and chloramphenicol against methicillin-resistant *Staphylococcus aureus*. J Glob Antimicrob Resist 2017, 10: 70-4.
23. Gustafson JE, Candelaria PV, Fisher SA, Goodridge JP, Lichocik TM, McWilliams TM, et al. Growth in the presence of salicylate increases fluoroquinolone resistance in *Staphylococcus aureus.* Antimicrob Agents Chemother 1999, 43: 990-2.
24. Alem MA, Douglas LJ. Effects of aspirin and other nonsteroidal anti-inflammatory drugs on biofilms and planktonic cells of *Candida albicans.* Antimicrob Agents Chemother 2004, 48: 41-7.
25. Zhou Y, Wang G, Li Y, Liu Y, Song Y, Zheng W, et al. *In vitro* interactions between aspirin and amphotericin B against planktonic cells and biofilm cells of *Candida albicans* and *C. parapsilosis.* Antimicrob Agents Chemother 2012, 56: 3250-60.
26. Krajewska-Kułak E, Niczyporuk W. Effects of the combination of ketoconazole and calcium channel antagonists against *Candida albicans in vitro.* Arzneimittel-Forschung 1993, 43: 782-3.
27. Liu S, Yue L, Gu W, Li X, Zhang L, Sun S. Synergistic effect of fluconazole and calcium channel blockers against resistant *Candida albicans.* PLoS One 2016, 11: 1-12.
28. Hu C, Li Y, Zhao Z, Wei S, Zhao Z, Chen H, et al. *In vitro* synergistic effect of amlodipine and imipenem on the expression of the AdeABC efflux pump in multidrug-resistant *Acinetobacter baumannii.* PloS One 2018, 13: 1-11.
29. Li Yj, Pan Cz, Zhao Zw, Zhao Zx, Chen Hl, Lu Wb. Effects of a combination of amlodipine and imipenem on 42 clinical isolates of *Acinetobacter baumannii* obtained from a teaching hospital in Guangzhou, China. BMC Infect Dis 2013, 13: 1-9.
30. Hennessy E, Mooij MJ, Legendre C, Reen FJ, O'Callaghan J, Adams C, et al. Statins inhibit *in vitro* virulence phenotypes of *Pseudomonas aeruginosa.* J Antibiot (Tokyo) 2013, 66: 99-101.
31. Kruszewska H, Zareba T, Tyski S. Examination of antibacterial and antifungal activity of selected non-antibiotic products. Act Pol Pharm Drug Res 2008, 65: 779-82.
32. Chen W, Wu T, Jiang S, Lv M, Fu J, Xia X, Zhang J. Clinical analysis of the effects of azole antifungal agents on the anticoagulant activity of warfarin. Medicine (Baltimore). 2020 Nov 13;99(46):e22987. doi: 10.1097/MD.0000000000022987.
33. Lima WG, Alves-Nascimento LA, Andrade JT, Vieira L, de Azambuja Ribeiro RIM, Thomé RG, Dos Santos HB, Ferreira JMS, Soares AC. Are the Statins promising antifungal agents against invasive candidiasis? Biomed Pharmacother. 2019 Mar;111:270-281. doi: 10.1016/j.biopha.2018.12.076.