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Drug interaction between antibiotics and anti-cancer drugs against some pathogenic bacteria

Raed A Muhammad[1], Muhsin A Essa[2]
[1] Directorate, Ministry of Education, Nineveh Education, Iraq
[2] Department of Biology, College of Science, University of Mosul, Mosul, Iraq

Abstract
The current study was conducted with the aim of investigating drug interaction between antibiotics and some anti-cancer drugs (Adriamycin (Doxorubicin), 5-Fluorouracil, Paclitaxel, Carboplatin) and their effect on the sensitivity of both *Staphylococcus aureus* and *Escherichia coli* against these antibiotics.
The results that the studied bacteria showed multiple resistance to antibiotics. also the results showed that the studied bacteria were highly sensitive to the anti-cancer drug (5-FU), compared to other anti-cancer drugs. The results of the interaction test between antibiotics and the anti-cancer drugs added to them generally show that they were divided into a synergistic reaction, an antagonistic reaction, or no significant interaction, depending on the type of drug and the type of bacteria, and that the *S. aureus* were more sensitive than the *E. coli* to various drug interactions. The drug (5-FU) was the most efficient in its synergistic activity with antibiotics compared to the rest of the drugs, Some anti-cancer drugs interact with antibiotics and reduce their antibacterial activity. Based on this result it is necessary for oncologists to create a treatment plan and consider potential drug interactions between anti-cancer treatment and antibiotics in order to ensure the best treatment for patients.

Keywords: Drug interactions, anticancer drugs, antibiotics, pathogenic bacteria, cancer

Introduction
Drug interactions are defined as those interactions in which the effects of a drug are changed by the presence of another drug at its site of action. These include additive interactions, synergistic interactions, antagonistic interactions, opposing interactions, and others (Van Leeuwen, 2016) [22]
Anticancer drugs are a class of pharmaceutical compounds that are used as a chemotherapeutic agent to treat cancer. They are organic compounds that prevent the proliferation of rapidly dividing cells or abnormal growth of any cell in tissues (Yadav *et al*., 2021) [25]
According to this property, anti-cancer drugs are known as "cytostatic" drugs. These drugs prevent DNA replication in the cell cycle by inhibiting the activity or action of the topoisomerase enzyme. However, due to their very low selectivity towards some cancer cell targets or because of their non-specific nature, these drugs contain Drugs also have a lot of negative effects on normal dividing cell (Novak *et al*., 2017) [14].
Because anticancer drugs are usually potent, toxic agents with low therapeutic efficacy, drug interactions are a major concern in oncology (Mathijssen *et al*., 2014) [12]. As they have been shown to be responsible for 20 to 30% of all adverse events and may be the cause of death in 4%. Of all cancer patients, others may be deprived of optimal anti-cancer treatment by reducing drug effects. In addition, since cancer patients often take many ancillary medications in addition to anti-cancer treatment, they are particularly at risk for drug interactions (Van Leeuwen, 2016) [22]. Therefore, appropriate cancer suppressive therapy combined with appropriate antimicrobials prolongs the lives of many patients suffering from malignant diseases. Therefore, it is important to understand the potential interactions between these drugs with regard to toxicity and activity. Although little is known, both synergism and antagonism between antibiotics and cytostatic drugs have been documented with regard to antibacterial efficacy (Nyhlén *et al*., 2002) [15].
Cancer patients are also more sensitive to bacterial infections due to both the disease and treatment with cytostatic drugs, and the most common types of pathogenic bacteria that colonize and cause infection in cancer patients are *Escherichia coli* and *Staphylococcus aureus* (Yan *et al*., 2023) [26].
The aim of the current study is to reveal the various drug interactions between antibiotics and some anti-cancer drugs and their effect on the sensitivity of both *S. aureus* and *E. coli* against these antibiotics.

Materials and methods
Bacterial isolates
Two types of pathogenic bacteria (*S. aureus*, *E. coli*) was used in the current study, isolated and diagnosed in the Department of biology /College of Science/University of Mosul, Iraq.

Antibiotics
In the current study, 12 different antibiotic discs were used, supplied by (Bioanalyse/ Turkey).
Azithromycin (AZM) 15µg/disc, Gentamicin (CN)10µg/disc, Tobramycin (TOB)10µg/disc, Levofloxacine (LEV) 5µg/disc, Cefixime (CFM)5µg/disc, Aztreonam (ATM)30µg/disc, Meropenem (MEM)10µg/disc, Imipenem (IPM) 10µg/disc, Ampicillin (AM) 25µg/disc, Cefepime (FEP) 10µg/disc, Ceftazidime (CAZ) 30µg/disc Ciprofloxacin (CIP) 10µg/disc.

Anti-cancer drugs
The studied anti-cancer drugs included four types obtained from local pharmacies in Mosul. city. Adriamycin (Doxorubicin)(Dox) 2mg/ml (Pfizer/Australia), 5-Fluorouracil(5-FU)50mg/ml (Onko/Turkey), Paclitaxel (Taxol)(PTX) 6mg/ml (Hospira/Australia), Carboplatin (CRBP) 10mg/ml (Accord/UK). Filter paper (0.45 mm) was

used to prepare sterile 5 mm diameter discs saturated with the above anti-cancer drugs.

Sensitivity of the studied bacteria to antibiotics and anti-cancer drugs test

Disc diffusion modified Kirby-Bauer method on Mueller-Hinton agar medium was used in this study. The Clinical and Laboratory Standards Institute (CLSI) guidelines used for interpretative the antibiotic results (Neel, 2012) [13]. As for anti-cancer drugs, the bacteria were considered sensitive when the diameter of the inhibition zone was greater than 8 mm (Montagna *et al*., 2019) [11].

Synergetic between antibiotics and anti-cancer drugs test

Synergy testing of anti-cancer drugs with antibiotics was conducted according to (Al-Ani and Al-Naimi, 2020). The antibiotic discs were fixed with sterile forceps on the surface of Mueller-Hinton agar medium inoculated with the studied bacterial isolates, then 10 microliters of each anti-cancer drug was added to each antibiotic disc, the plates were incubated at 37°C for 24 hours, and the diameters of inhibition were measured. The results were calculated based on the fact that the synergistic effect is an increase in the diameter of inhibition for both antibiotics and anti-cancer drugs together compared to the diameter of inhibition for each of them separately (Al-Taee, 2013).

Results

Table (1) and Figure (1) show the results of testing the sensitivity of bacterial isolates to 12 various antibiotics. It is noted that the studied bacteria showed multiple resistance to antibiotics.

Table 1: Antibiotics sensitivity results. (diameter of inhibition in mm)

Isolates	Antibiotics											
	AM	FEB	AZM	CIP	MEM	ATM	TOB	CN	LEV	IPM	CAZ	CFM
S. aureus	R(0)	R(0)	S(25)	R(14)	S(29)	R(0)	S(18)	S(17)	R(13)	S(40)	R(13)	R(14)
E. coli	R(0)	R(0)	I(14)	R(15)	S(32)	R(14)	I(14)	R(13)	R(13)	S(31)	R(10)	R(0)

Resistant: R, Sensitive: S, Intermediate: I

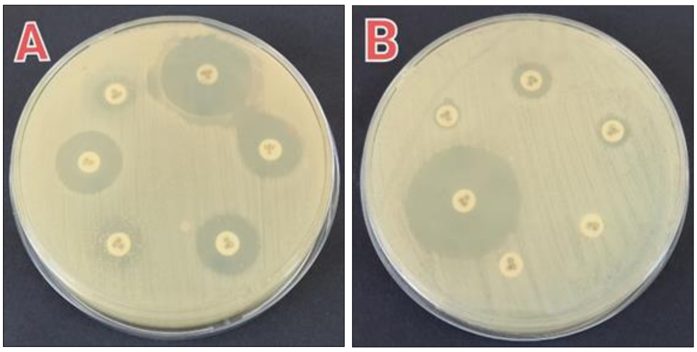

Fig1: Sensitivity of the studied bacteria toward antibiotics: (A) *S. aureus*(B) *E.* coli

The results in Table (2) and Figure (2) show the sensitivity of the studied bacteria to anti-cancer drugs .The results showed that the inhibitory activity of the drug 5-Fluorouracil (5-FU) was very high, as it showed an inhibitory effect against the two types of studied bacteria, while the drug Doxorubicin(DOX) showed inhibitory activity against *S.aureus* and did not show any inhibitory activity against *E.coli*, and the rest of the drugs , Paclitaxel (PTX) Carboplatin (CRBP) did not show any inhibitory activity against the studied bacteria.

Table 2: The sensitivity of the studied bacteria to different Anticancer drugs (diameter of inhibition in mm)

Isolates	Anti-cancer drugs			
	5FU	PTX	DOX	CRBP
S. aureus	S(52)	R(0)	S(16)	R(0)
E. coli	S(50)	R(0)	R(0)	R(0)

Resistant: R, Sensitive: S

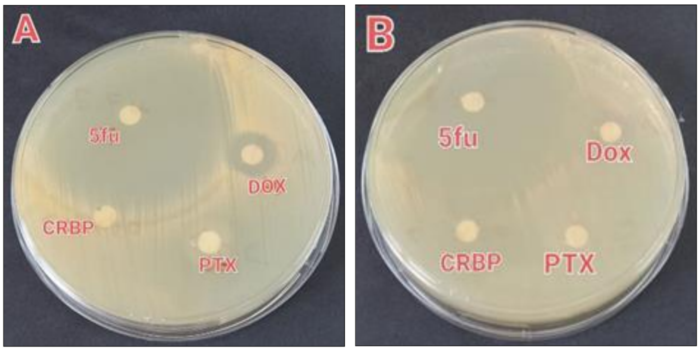

Fig 2: Inhibitory effect of anticancer drugs on (A): *S. aureus*(B): *E.* coli

Table (3) and Figure (3)(4) show the results of interaction test of antibiotics and the anti-cancer drugs added to them. The results show a synergistic interaction between the anticancer drug (5-FU) with all types of antibiotics that showed bacteria resistance to it, and an increase in the inhibitory diameter of the antibiotic against sensitive bacteria, with the exception of the antagonistic reaction with IPM against *S. aureus* bacteria. Some studies indicate that synergistic effect is significant when it is equal to 5 mm or more (Adwan and Mhanna, 2008; Stefanovic and Comic, 2012) [2, 19].

The drug (PTX) showed a synergistic interaction with four antibiotics (FEB, MEM, ATM, IPM) and an antagonistic effect with (CAZ, CFM). It did not show any interaction with antibiotics (AZM, TOB, CN, LEV, CIP, AM) Against the *S. aureus*. while it showed a synergistic interaction with the antibiotics (FEB, AM) and an antagonistic interaction with (IPM, TOB, CN, LEV CFM, CIP, CAZ), it did not show any interaction with the antibiotics (AZM, MEM, ATM) against the *E. coli*. As for the drug (DOX), it showed a synergistic interaction with antibiotics (IPM, MEM, ATM, LEV, FEB, AM) and an antagonistic interaction with the antibiotic (CFM), and did not show any interaction with antibiotics (AZM, TOB, CN, CAZ, CIP) Against the *S. aureus*. while no synergistic interaction appeared with all the antibiotics studied, it showed an antagonistic interaction with the antibiotics (CN, LEV, CIP) and did not show any interaction with the antibiotics (AZM, MEM, TOB, CAZ, AM, FEB, IPM, CFM, ATM) against *E. coli*. As for the drug (CRBP), it showed a synergistic interaction with the antibiotics (LEV, MEM), an antagonistic interaction with the antibiotics (CN, TOB, CIP, AZM, CFM, CAZ, IPM), and no interaction with the antibiotics (AM, FEB, ATM) towards *S. aureus*. While it showed a synergistic interaction with the antibiotics (AM, FEB, CFM), an antagonistic interaction with the antibiotics (IPM CAZ, LEV, CIP), and no interaction with the antibiotics (TOB, ATM, CN, MEM, AZM,) towards the *E. coli*.

Table3: Interaction effect between antibiotics and anticancer drugs against the studied bacteria. (diameter of inhibition in mm)

Isolates	Anti-cancer drugs	Antibiotics											
		AM	FEB	AZM	CIP	MEM	ATM	TOB	CN	LEV	IPM	CAZ	CFM
S. aureus	5FU	S (30)	S (31)	S (30)	S (35)	S (40)	S (40)	S (35)	S (28)	S (35)	A(38)	S(34)	S(30)
	PTX	N (0)	S(9)	N (28)	N (15)	S(35)	S(10)	N (9)	N (10)	N (12)	S(45)	A(10)	A(10)
	DOX	(11) S	S(10)	N (25)	N (15)	S(34)	S(13)	N (18)	N (17)	S(21)	S(45)	N (13)	A(12)
	CRBP	N (0)	N (0)	A(21)	A(10)	S(35)	N (0)	A(0)	A(0)	S(28)	A(22)	A(12)	A(9)
E. coli	5FU	S(32)	S(36)	S(38)	S(36)	S(42)	S(36)	S(30)	S(32)	S(33)	S(37)	S(34)	S(33)
	PTX	S(9)	S(9)	N (16)	A(13)	N (33)	N (14)	A(13)	A(11)	A(12)	A(30)	A(12)	A(8)
	DOX	N (0)	N (0)	N (16)	A(14)	N (33)	N (14)	N (15)	A(11)	A(11)	N (31)	N (11)	N (0)
	CRBP	S(9)	S(9)	N (16)	A(13)	N (32)	N (14)	N (15)	N (13)	A(12)	A(29)	A(11)	S(8)

S: Synergistic, A: Antagonistic, N: Neutral (No reaction)

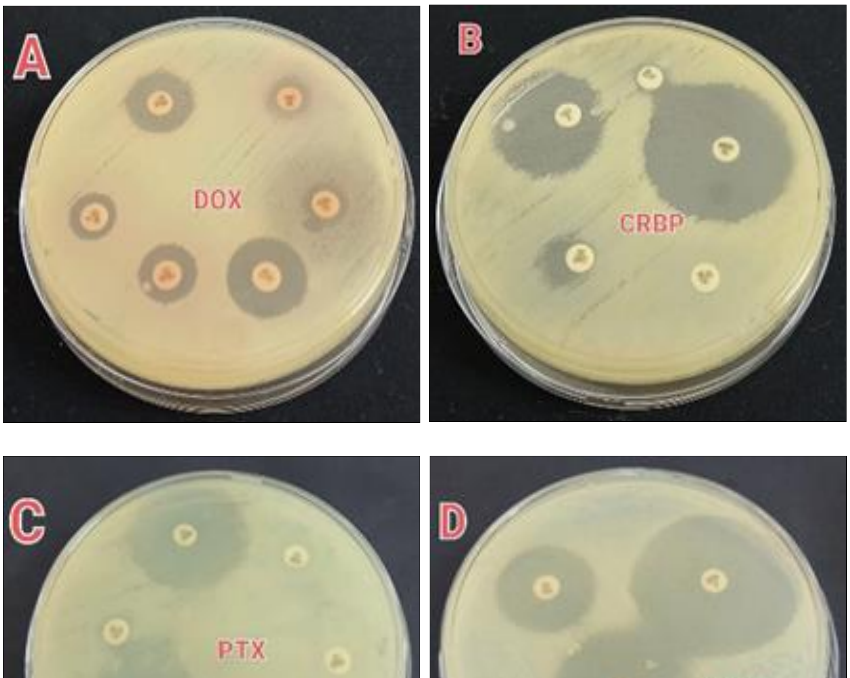

Fig 3: Interaction of antibiotic with anti-cancer drugs in *S. aureus*

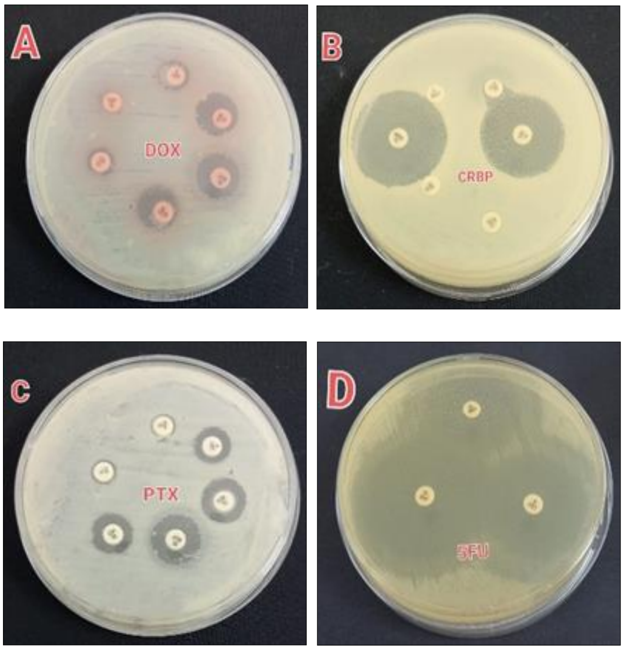

Fig 4: Interaction of antibiotic with anti-cancer drugs in *E.* coli

Discussion

It is noted from the results of the antibiotic sensitivity test that the studied bacteria showed multiple resistance to antibiotics, as the excessive and indiscriminate use of antibiotics leads to the spread of resistance among bacteria due to the phenomenon of natural selection (Bottery *et al*., 2021) [6]. The emergence of multiple resistant bacteria to common conventional antibiotics is a serious health problem, as this problem has increased widely and significantly in recent decades (WHO, 2019). The resistance of studied bacteria to antibiotics is one of the important health problems, as they are among hospital acquired infection microbes that are widespread in high rates and cause a wide range of infections, with a high mortality rate (Adekunle *et al*., 2022; Jahan *et al*., 2022) [1, 8].

The results of the sensitivity test towards cancer drugs showed that the studied bacteria were highly sensitive to the anti-cancer drug (5-FU), which reflects the great antimicrobial activity that this drug possesses and its effect on both types of Gram-positive and Gram-negative bacteria, while the drug (DOX) showed an inhibitory effect on *S.aureus* and did not show any effect on *E.coli*, as some studies confirm that this drug may interfere with cell division, and perhaps this explains its mechanism of action as an antibacterial (Panda *et al*., 2015) [16].

The anti-cancer drugs (CRBP, PTX) did not show anti-bacterial activity against the studied bacteria, this may be due to the fact that they do not contain compounds that affect the various activities of bacteria. Some drugs, such as (5-FU) and (DOX), seem to have a more pronounced antibacterial effect than other antitumor drugs, and some bacteria are more sensitive to anticancer drugs than others (Kvakkestad *et al*., 2012) [9].

The results of the interaction test between antibiotics and the anti-cancer drugs added to them generally show that they were divided into a synergistic reaction, an antagonistic reaction, or no significant interaction, depending on the type of drug and the type of bacteria, and that the *S. aureus* were more sensitive than the *E. coli* to various drug interactions. Most studies reported that the sensitivity of bacteria to anti-cancer drugs and the interaction between antibiotics and anti-cancer drugs often differ significantly between bacterial species and even between strains of the same species, so such interactions must be dealt with for each type and combined between them separately (Bergstrom *et al*., 1994) [5].

The drug (5-FU) was the most efficient in its synergistic activity with antibiotics compared to the rest of the drugs, and many previous studies agree with this result, especially with beta-lactam antibiotics (Ueda *et al*., 1983; Gieringer *et al*., 1986) [21, 7]. The significant synergistic effect of the drug (5-FU) with antibiotics and converting resistant bacteria into antibiotic-sensitive ones may can be explained by the formation of a new structure or complex that is more effective in inhibiting or killing bacteria (Ahmed *et al*., 2010) [4]. The presence of (5-FU) with aminoglycoside antibiotics increases the lethal effect of these antibiotics against *S.aureus* (Nyhlén *et al*., 2002) [15]. The synergistic effect of the drug (5-FU) may have resulted from inhibiting the formation of DNA, as (5-FU) causes the breakdown of thymine in bacteria by inhibiting the thymidylate synthase enzyme required for DNA formation. Its synergistic effect may also result from causing a disturbance in osmotic regulation, which facilitates the entry of antibiotic molecules into the cell and reaching their targets (Patil *et al*., 2023) [17].

Doxorubicin inhibits bacterial growth through mechanisms similar to those that cause cytotoxicity in humans, particularly inducing DNA and RNA damage (Westman *et al*., 2012) [24]. Its effect on bacterial DNA may have facilitated the action of some antibodies, leading to a synergistic effect between them.

Some anti-cancer drugs may interact with antibiotics and reduce their antibacterial effectiveness. Such interactions increase the risk of bacterial infection and thus increase the mortality rate related to chemotherapy (Turossi-Amorim *et al*., 2022) [20]. This is consistent with the current study in terms of the presence of antagonistic interactions between some anti-cancer drugs and some Antibiotics shown in Table (3). Therefore, it is necessary for oncologists to create a treatment plan and consider potential drug interactions between anti-cancer treatment and antibiotics in order to ensure the best treatment for patients.

The anti-cancer drugs CRBP and PTX do not have an effect on bacteria alone, but when combined with some antibiotics, they show a synergistic or antagonistic effect depending on the type of antibiotic. This is due to the fact that some drug interactions occur between antibiotics and compounds that do not have antimicrobial activity, but these Compounds can work., for example, increase or decrease the effect of antibiotics (Pieren and Tigges, 2012) [18].

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