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University of Basra
College of pharmacy

Study of the Antibacterial efficacy of cefixime produce from different companies'

Submitted to the Council of College of Pharmacy in Partial Fulfillment of the Requirements for the Bachelor's Degree

By

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بِسْمِ اللهِ الرَّحْمَنِ الرَّحِيمِ

اقْرَأْ بِاسْمِ رَبِّكَ الَّذِي خَلَقَ (1) خَلَقَ الإِنْسَانَ مِنْ عَلَقٍ

(2) اقْرَأْ وَرَبُّكَ الأَكْرَمُ (3) الَّذِي عَلَّمَ بِالْقَلَمِ (4) عَلَّمَ

الإِنْسَانَ مَا لَمْ يَعْلَمْ (5)

صدق الله العلي العظيم

(سورة العلق - الاية 9)

الاهداءِ

الى من بلغ الرسالة وأدى الامانة ونصح الامة .. الى نبي ا لرحمة ونور العالمين .. سيدنا محمد صلى الله عليه واله وسلم تسليماً كثيرا ...

إلى صاحب السيرة العطرة، والفكر المُستنير .... والدي الحبيب

إلى من وضع المولى الجنة تحت قدميها، ووقَّرها في كتابه العزيز .... أمي الحبيبة

إلى من كان لهم بالغ الأثر في كثير من العقبات والصعاب إلى من أعتمد عليهم في كل كبيرة وصغيرة .... إخواني وإخوتي

الى كل من يرى ان العلم نور الحياة .... احتراماً

اهدي جهدي المتواضع

شكر وتقدير

نود أن نعرب عن شكرنا لمشرف هذهِ الدراسة *الدكتور زهير الشاهين* لإشرافه الدقيق والقيّم طوال الدراسة ولجهوده الكبيرة في إكمال بحث مفيد علميًا.

كما نود أن نشكر *الدكتورة سهى هيثم* على مساعدتها ومتابعتها والتدقيق المستمر لخطوات العمل.

كل الاحترام

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Abstract

Cefixime , is an antibiotic medication used to treat a number of bacterial infections. These infections include otitis media, strep throat, pneumonia, urinary tract infections, gonorrhea, and Lyme disease. For gonorrhea typically only one dose is required.

The objective is to compare the antibacterial activity of different brands 1 , 2 ,3 of cefixime against *Staphylococcus aureus* and *Escherichia coli* which they were cultured in Mueller-Hinton media . Preparation of stock solutions and diluted solutions from different brands of cefixime (diluted solutions with different concentrations 1000.500,250 and 125 µg/ ml) . After that add different concentrations to the bacterial culture using disk diffusion method and incubated for 24 hours. After incubation period measurement inhibition zone of different concentration in mm and determine the minimum inhibitory concentration of each brands .The result of all plates test show clear inhibition for growth of *Staphylococcus aureus* by cefixime and *Escherichia coli* have been inhibited only but in higher concentrations only . The study revealed MIC show by brand 3 which give higher inhibition at 125 µg/ ml than other brands.

Chapter One
Introduction and Literature Review

Introduction and Literature Review

1.1Introduction

Antibiotics are the group of medicines that are produced by microorganisms or formulated synthetically; they have dynamic property of inhibiting bacterial growth or completely suppressing the toxic effects of microorganisms. Accessibility of commercially available broad spectrum antibiotics causing multi drug resistance remains a key global health issue (Khan et al., 2011).

In recent years, the increased use of drugs and indiscriminately has given serious results and encouraged the emergence of bacterial strains resistant to many antibiotics with increasing death (WHO, 2001). Resistance of these organisms are called Multiple Drugs Resistance (MDR) which has become increasingly important as a health problem. These organisms are resistant to three or more of the drug classes naturally by having different mechanisms and are able to develop resistance to all effective antimicrobial drugs (Gad et al., 2007). Microbial resistance can affect clinical results and therefore, there will be a difficulty in choosing the appropriate treatment for the patients and this may extend to the length of the patient's stay in hospital with continued infection (Cosgrove, 2006). Antibiotics are the group of medicines that are produced by microorganisms or formulated synthetically; they have dynamic property of inhibiting bacterial growth or completely suppressing the toxic effects of microorganisms.

Escherichia coli is a common pathogen linked with community- associated as well as nosocomial infections (Oteo et al., 2005; Drago et al., 2010). In the last few years, the emergence and wide dissemination of *E. coli* strains showing resistance to broad-spectrum of antimicrobial agents has been reported (Sahm et al., 2001; Oteo et al., 2005; Bartoloni et al., 2006). Emergence of resistance to multiple antimicrobial agents in pathogenic bacteria has become a significant public health threat as there are fewer, or even sometimes no, effective antimicrobial agents available for infections caused by these bacteria (Oteo et al., 2001; Sahm et al., 2001; Bartoloni et al., 2006; Magiorakos et al., 2011).

Multiple antibiotic resistance is a major health concern in the treatment of staphylococcal infections, especially infections of *methicillin-resistant S. aureus* (MRSA) which occurs due to the extensive use of antimicrobial agents, coupled with the transmission of an appreciable proportion of the organism by person-to-person contacts (4). Hence, effective control of antibiotic use and prevention of the transmission of these strains are essential to eradicate this infectious organism. In this study, we use clinically isolated gram positive bacteria (*Staphylococcus aureus*) and gram negative bacteria (*Escherichia coli*).

- Hence in this study the drug used for investigation is Cefixime, which is characterized as a broad spectrum antibiotic (Anacona and Estacio, 2006).

Cefixime is a B-lactamase stable third generation cephalosporin, which is a semi- synthetic compound and was the first orally active and effective antibiotic with longest half life (Rafal'skii et al., 2011, Wilson and Gisvold's, 1998 and Wu, 1993). Cefixime has very significant biological properties, as it exhibits potent antibacterial activity against a varied range of different strains of bacteria.

1.2 The aim

The clinical efficacy for each drug product can be ensured when quality is reliable and reproducible . With appropriate and correct use of antibiotics there will be less of resistance of bacteria . Cefixime is one of antibiotics which have spectrum and much use in the community , so have higher chance for develop resistance due to highly use or inappropriate use .

In our study the aim is to compare the antibacterial activity of Cefixime against clinically isolated bacteria (*Staphylococcus aureus* and *Escherichia coli*) produce identification from different companies'.

1.3 Literature Review

1.3.1 Multiple Drug Resistance (MDR)

Multiple drug resistance (MDR), multidrug resistance or multiresistance is antimicrobial resistance shown by a species of microorganism to at least one antimicrobial drug in three or more antimicrobial categories (Magiorakos et al. 2011). Antimicrobial categories are classifications of antimicrobial agents based on their mode of action and specific to target organisms (Magiorakos et al. 2011). The MDR types most threatening to public health are MDR bacteria that resist multiple antibiotics; other types include MDR viruses, parasites (resistant to multiple antifungal, antiviral, and antiparasitic drugs of a wide chemical variety).

1.3.2 Bacterial resistance to antibiotics

Various microorganisms have survived for thousands of years by their ability to adapt to antimicrobial agents. They do so via spontaneous mutation or by DNA transfer. This process enables some bacteria to oppose the action of certain antibiotics, rendering the antibiotics ineffective.[4] These microorganisms employ several mechanisms in attaining multi-drug resistance (Stix, 2006; Li et al., 2009; Periasamy et al., 2020): Enzymatic deactivation of antibiotics, Decreased cell wall permeability to antibiotics, Altered target sites of antibiotic, Efflux mechanisms to remove antibiotics, and Increased mutation rate as a stress response.

Many different bacteria now exhibit multi-drug resistance, including *staphylococci*, *enterococci*, *gonococci*, *streptococci*, *salmonella*, as well as numerous other *Gram-negative bacteria* and *Mycobacterium tuberculosis*. Antibiotic resistant bacteria are able to transfer copies of DNA that code for a mechanism of resistance to other bacteria even distantly related to them, which then are also able to pass on the resistance genes and so generations of antibiotics resistant bacteria are produced (Hussain and Pakistan, 2015). This process is called horizontal gene transfer and is mediated through cell-cell conjugation.

1.3.3 Morphology of *Escherichia coli*

E. coli is a Gram-negative, facultative anaerobe, nonsporulating coliform bacterium.[18] Cells are typically rod-shaped, and are about 2.0 μm long and 0.25–1.0 μm in diameter, with a cell volume of 0.6– 0.7 μm3 (Kubitschek, 1990; Yu et al., 2014).

E. coli stains Gram- negative because its cell wall is composed of a thin

peptidoglycan layer and an outer membrane.
During the staining process, *E. coli* picks up the color of the counterstain safranin and stains pink. The outer membrane surrounding the cell wall provides a barrier to certain antibiotics such that *E. coli* is not damaged by penicillin (Tortora, 2010). The flagella which allow the bacteria to swim have a peritrichous arrangement (Darnton et al., 2007). It also attaches and effaces to the microvilli of the intestines via an adhesion molecule known as intimin.

1.3.4 Morphology of *Staphylococcus aureus*

Staphylococcus aureus is a Gram-positive spherically shaped bacterium, a member of the Bacillota, and is a usual member of the microbiota of the body, frequently found in the upper respiratory tract and on the skin. It is often positive for catalase and nitrate reduction and is a facultative anaerobe that can grow without the need for oxygen (Masalha et al., 2001). Although *S. aureus* usually acts as a commensal of the human microbiota, it can also become an opportunistic pathogen, being a common cause of skin infections including abscesses, respiratory infections such as sinusitis, and food poisoning. Pathogenic strains often promote infections by producing virulence factors such as potent protein toxins, and the expression of a cell-surface protein that binds and inactivates antibodies. *S. aureus* is one of the leading pathogens for deaths associated with antimicrobial resistance and the emergence of antibiotic-resistant strains, such as *methicillin-resistant S. aureus (MRSA),* is a worldwide problem in clinical medicine. Despite much research and development, no vaccine for *S. aureus* has been approved.

It is produces two main types of soluble pigments which are pyocyanin and pyoverdin, the latter plays an important role in iron metabolism and is produced abundantly in media with low ironcontent. Pyocyanin pigments are called blue pus, this is a feature of supportive infections attributed to P. aeruginosa (Gilligan, 1991). Also, it produces other pigments such as pyorubin and pyomelanin (Bergey's Manual of Systematic Bacteriology, 2001).

1.3.6 Resistance of Bacteria

Antibiotics have had great success and have been instrumental in protecting millions of patients and controlling many diseases, but their increased and indiscriminate use encouraged the emergence of microbial strains resistant to many antibiotics. Antibiotic resistance is a serious health problem that is life-threatening and can leads to serious results (Olayinka et al., 2004).

In recent years, there has been an increase in the number of bacterial strains resistant to treatment. It is possible to identify multidrug resistant (MDR) as resistance of the microorganism and insensitivity to more than three classes of antibiotics during the period of exposure to treatment against infection (Singh, 2003 ; Popęda et al., 2014). The resistance that is shown by these microorganisms leads the ineffective action of antibiotic in the treatment of clinical conditions, thus a failure in working on the target and spread of infection significantly. The major risk that encounter the patient in the hospital is the spread of these strains among patients, especially patients with impaired immune system and have no ability to resist infection (Loeb et al., 2003).

1.3.7 Cefixime

Cefixime is a B-lactamase stable third generation cephalosporin, which is a semi-synthetic compound and was the first orally active and effective antibiotic with longest half life (Rafal'skii et al., 2011, Wilson and Gisvold's, 1998 and Wu, 1993). Cefixime has very significant biological properties, as it exhibits potent antibacterial activity against a varied range of different strains of bacteria. Previous researches have reported Cefixime as a nontoxic and effective oral therapeutic especially in case of multidrug-resistance (Memon et al., 1997). The chemical structure of Cefixime (Figure 2-1) having molecular formula C16H15N5O7S2, with molecular weight 453.4, consists of the Cephem nucleus, in which a ring of □-lactam is fused to a 6- membered di-hydro-thiazine ring (Gelone and O'Donnell, 2005). The basic ring structure incorporates two major modifications; Cephem nucleus conatins Vinyl group at 3rd position which is responsible for appropriate absorption in the intestine, the permeation of the drug occurs by a carrier mediated transport mechanism (Naqvi et al., 2011). The antibacterial activity of Cefixime is due to aminothiazole ring and the R-OXy amino group present on the side chain at the 7-position in its chemical structure (Rafal'skii et al., 2011). Evidences also report that Cefixime produces the antibacterial activity by inhibiting peptidoglycan synthesis in the bacterial cell wall (Petri, 2006). Conventionally Cefixime has been used in the treatment of respiratory tract infections (Kunel'skaya et al., 2008 and Edelstein et al., 1993) urinary tract infections (Rafal'skii et al., 2011 and Dagan et al., 1992) gonorrhea (Ison and Alexander, 2011) and typhoid fever (Barry et al., 1994). Cefixime has significant activity against Group A and B hemolytic

Streptococci and Streptococcus pneumonia (Barry et al., 1994). Neisseria gonorrheae and Haemophilus influenzae are also Cefixime sensitive even in the presence of beta-lactamase enzyme (Mortensen and Himes, 1990 and Nash et al., 1991).

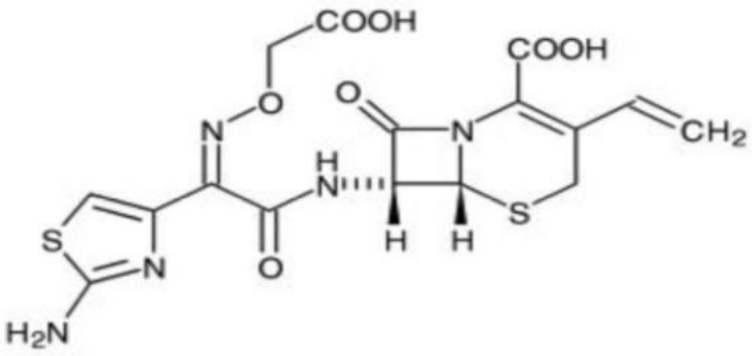

Fig.1: Chemical structure of *Cefixime*.

1.3.8 Mechanism Action of Cefixime

The antibacterial effect of cefixime results from inhibition of mucopeptide synthesis in the bacterial cell wall. Like all beta-lactam antibiotics, cefixime binds to specific penicillin-binding proteins (PBPs) located inside the bacterial cell wall, causing the inhibition of the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that cefixime interferes with an autolysin inhibitor. The pharmacokinetics of cefixime were determined in adult and pediatric subjects.

In general the half-life of the drug is about 3 to 4 hours and is not dependent on dose. The drug is not extensively bound to serum proteins; the free fraction is about 31% and is concentration-independent. The absolute bioavailability, based on comparisons of area under the serum concentration-time curve values after 200-mg intravenous, 200-mg oral solution, and 200- and 400-mg capsule doses, ranged from 40 to 52%, showing a comparable bioavailability for cefixime at single 200- and 400-mg oral doses (Faulkner RD , Pediatr Infect Dis J. 1987).

1.3.9 Pharmacokinetic Properties

Following **oral administration** peak plasma concentrations of cefixime are generally attained in 3 or 4 hours and are about 2.0 to 2.6 mg/L (mean) after a single 200mg dose. Other than a delay to peak plasma concentrations the pharmacokinetics of cefixime are not influenced by food. There is no evidence of drug accumulation following administration of 200mg twice daily or 400mg once

daily for 15 days. In children, the pharmacokinetics of cefixime 8 mg/kg were similar to those observed in adults given a 400mg capsule dose. The calculated absolute bioavailability of cefixime was 40% for 400mg capsules, 48% for 200mg capsules and 52% for an oral solution.
No biologically active metabolites of cefixime have been identified in plasma or urine and an average of about 12 to 20% of a 200mg dose is recovered unchanged in the urine over 24 hours.

1.3.10 Adverse Effects

Clinical adverse experiences reported by investigators in patients treated with cefixime have usually been mild to moderate in severity, and transient. Diarrhoea and stool changes (as distinct from diarrhoea) have been the most commonly reported adverse effects, occurring in 13.8 and 13.5% of patients, respectively. Diarrhoea tended to be more frequent following once daily (15.3%) than twice daily (10.3%) administration in adults, but this trend was not apparent in children. In about two-thirds of instances diarrhoea and stool changes were evident within 4 days of beginning treatment, which is contrary to the pattern usually encountered with changes in bowel flora. Comparative trials conducted in the USA revealed a greater frequency of diarrhoea and stool changes with cefixime than with amoxycillin, while other gastrointestinal complaints occurred with similar frequency with both drugs.

1.3.11 Dosage and Administration

The usual adult dosage is 400mg daily administered as a single dose or in 2 equally divided doses. A lower dosage of 200mg daily has been used in uncomplicated urinary tract infections. In children, cefixime 8 mg/kg/day once daily or in 2 divided doses has been the most widely used dosage for treating acute otitis media, acute tonsillitis and acute pharyngitis. In patients with severe renal dysfunction (creatinine clearance <20 ml/min) half the standard dose of cefixime should be administered once daily.

Chapter Two
Methods

Materials and Methods

2.1 Tools & Material

Tools	Material
Conical flask	Mueller- Hinton powder
Cylinder	distill water
Petri dish	DMSO
Hot plate	Cefixime drug 1-2-3 different brand companies
Inoculation loop	alcohol 70%
L-shape spreader	
Cork borer	
Sensitive scale	
Electrical balance	
Autoclave	
Incubator	
Syringes	
Forceps	
Test tubes	

Table 1 : tools and materials

2.2 Procedure

2.2.1 Test Organisms

Strains of Staphylococcus aureus and Pseudomonas aeruginosa were isolated and cultured by Clinical Laboratory Sciences Department, University of Basra.

2.2.2 preparation of stock solution

- weight the 3 brands of cefixime capsules with shell and without the shell
- calculate the main weight of active ingredient cefixime by subtracting the weight without the shell from the weight with the shell.
- take 5 mg of cefixime and dissolve in 2 ml of DMSO and 3 ml of D.W to prepare the stock solution for each brand.

2.2.3 Prepare The dilute Solutions

- Prepare from each brand 5 concentrations
-1ST diluenttomake1000 µg(take1ml of stock in one container).
- 2nd Diluent to make 500 µg (take 1 ml of 1st solution and 1 ml of of water) in one container.
- 3rd diluent to make 250 µg(by take 1 ml of 2nd diluents and 1 ml of water)
- 4th diluent to make 125 µg(by take 1ml of 3rd diluent and 1 ml of water)

So , here we have 4 solution for each brand .

2.2.4 Preparation Mueller Hinton Agar

- Suspend 9.5 g of your Mueller Hinton Agar powder in 250 ml of distilled water.
- Mix and dissolve them completely.
- Sterilize by autoclaving at 121°C for 28 minutes.
- Pour the liquid into the petri dish and wait for the medium to solidify.
- Must sure that you are preparing the agar in the clean environment to prevent any contamination.

2.3 Determination of zone of inhibition

The **disk diffusion method** is based on the determination of the zone of inhibition (ZI) proportional to the bacterial susceptibility to the antimicrobial present in the disk. The diameter of this ZI around the antimicrobial disk depends on the concentration of antibiotics in the disk and its diffusibility.

1. First, we must refresh the bacteria on the agar plates a day before the process of introducing the antibiotic solution into the agar plate.
2. The agar plate was inoculated with 200µL of the test bacteria and an L- shaped spreader was used to spread the microbial inoculum across the entire agar surface. The whole procedure was carried out under aseptic conditions near the flame.
3. MH agar plates were appropriately labelled for each organism to be tested with the names and concentrations of drug made. The labelling was made on the outer layer of the bottom of petri dish.
4. Placement of the antibiotic disks was carried out on the next day. Disks were added one at a time to the agar plate using forceps. Sterilize the forceps by cleaning them with a sterile alcohol pad and allowing them to dry or immersing the forceps in alcohol then igniting.
5. The lid of the petri dish was partially removed, and the disks were placed over the marked spots that were made earlier, and gently pressed to ensure complete adherence with the agar surface. The lid of the plate was replaced between disks to minimize exposure to airborne contaminants. Placing the disks close to the edge of the plate was avoided as the zones will not be fully round and can be difficult to measure.
6. The plates were then incubated at a temperature range of 35°C ± 2°C for 24 hrs.
7. After appropriate incubation, the plates were observed, and the inhibition zone diameter was measured and recorded for determination of MIC. This procedure was carried out for each of the 3 brands of antibiotic.

Chapter Three
Results and Discussion

3.1 Result and Discussion

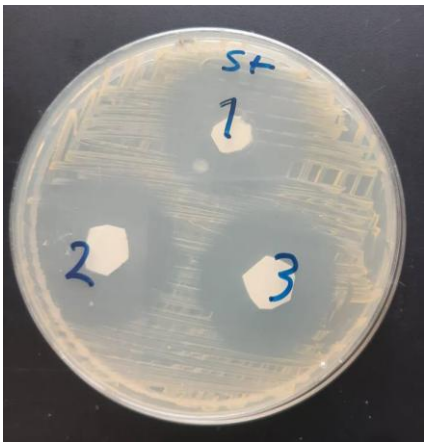

Figure 3.1 : Inhibition zone of 3 brands in1000 µg/ml of *S. aureus.*

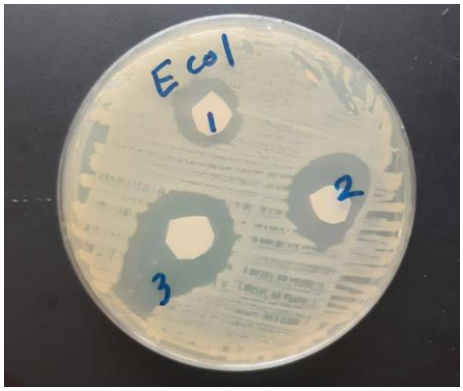

Figure 3.2 : Inhibition zone of 3 brands in1000 µg/ml of *E. coli*

Figure 3.3 : Inhibition zones of brand 1 in 500,250,125 µg/ml of *S. aureus.*

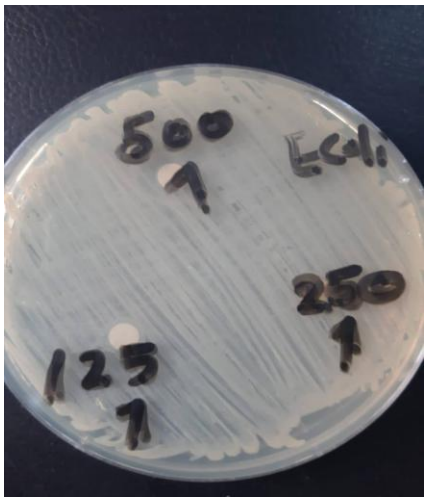

Figure 3.4 : inhibition zones of brand 1 in 500,250,125 µg/ml of *E. coli.*

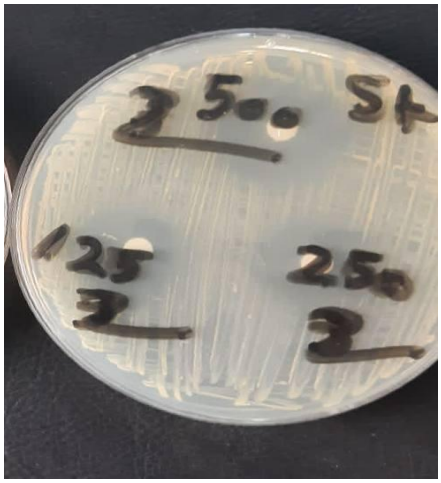

Figure 3.5 : Inhibition zones of brand 2 in 500,250,125 µg/ml of *S. aureus.*

Figure 3.6 : inhibition zones of brand 2 in 500,250,125 µg/ml of *E. coli.*

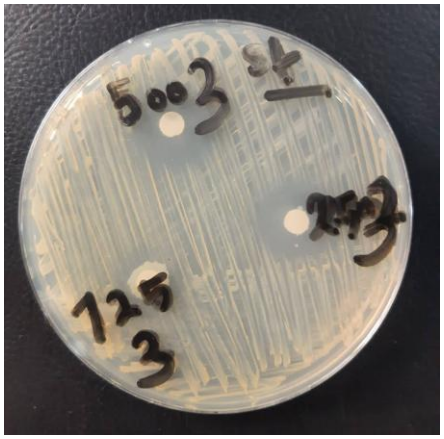

Figure 3.7 :Inhibition zones of brand 3 in 500,250,125 µg/ml of *S. aureus*.

Figure 3.7 : inhibition zones of brand 3 in 500,250,125 µg/ml of *E. coli*.

From the results it is concluded with no reservation that the3 brands of Cefixime (purchased from the market) possess similar antibacterial activity as compared with each other but the brand 3 shows some differences in inhibition zone as tables below

Brand 1	*S. aureus*				*E. coli*			
	Concentration (µg/ml)							
	1000	500	250	125	1000	500	250	125
	Diameter (mm)							
	30	19	Zero	Zero	20	10	Zero	Zero

Table 2 : result of brand 1

Brand 2	*S. aureus*				*E. coli*			
	Concentration (µg/ml)							
	1000	500	250	125	1000	500	250	125
	Diameter (mm)							
	33	25	22	20	22	10	Zero	Zero

Table 3 : result of brand 2

	S. aureus				*E. coli*			
	Concentration (µg/ml)							
Brand 3	1000	500	250	125	1000	500	250	125
	Diameter (mm)							
	33	20	19	15	25	10	Zero	Zero

Table 4 : result of brand 3

Discussion

After literature review the concept of our present study was novel as the determination of the use of an antibiotic for treatment of bacterial infection relies upon the information collected by susceptibility test conducted on infecting microorganism (Gennaro, 1985). Analysis of antibacterial activity has traditionally been conducted In Vitro quite frequently, because results of these susceptibility tests can be used to determine how a drug would act inside the body (Hannan et al., 2008). Resistance of virulent microorganisms to antibiotics has been a major concern for a long period (Gums, 2002) therefore the purpose of the current study was to evaluate the antibacterial activity of different commercially available brands of Cefixime in the market against isolates of selected organisms i.e., E. coli and S. aureus . The antibiotic susceptibility test is one of the important tests to determine the resistance and sensitivity of bacteria that are important for clinical purposes (Aruna et al., 2010). The study of bacterial resistance to multiple antibiotics is crucial in deciding on the appropriate treatment for the infection resulting from it as the spread of these MDR bacterial strains poses a great risk to the health of individuals of all ages. (cefixime) is a cephalosporin antibiotic used to treat many different types of infections caused by bacteria. Our study of susceptibility pattern tests of certain antibiotics on standard ATCC and clinical isolate of E.coli And S.aureus and was conducted using different brands of cefixime. The E.coli show resistant to this antibiotics(cefixime) in concentrations that we use (500, 250,125,, µg) and inhibits from concentration 1000 micro just.staphylococcus show inhibits from this antibiotic (cefixime) in all concentrations that we use (1000,500, 250,125, µg) All bacterial isolates showed high inhibition from Cefixime. But the brand 3 have some different in inhibition zone from other may be because the formulation process or may be because adding different excipients .

One of the main reasons for this resistance is due to the frequent use of antibiotics, especially the broad spectrum, in addition to the existence of strains resistant to treatment continuously and moving from one patient to another.

Failure to prevent the transmission of this infection among patients in the development of drug-resistant strains, as well as the length of stay in the hospital, makes it a suitable environment for microbes. A structured protocol for the use of antibiotics should be adopted and ways should be found to avoid the spread of resistant bacteria .

Conclusion

Conclusion

From the results it is concluded with no reservation that the 3 brands of Cefixime All three brands of capsules exhibited potent antibacterial effect as indicated by production of zones of growth inhibition against both test bacteria. But the clinical isolation of *E.coli* shows resistance in low concentrations and needs high concentrations to show inhibition from this antibacterial agent (cefixime) The proximity in diameters of ZI produced is a good marker that the three brands are efficacious.

• We show some resistant bacteria were encountered during our tests in *Ecoli* . This indicates that the clinical isolates of both *S. aureus* have developed no resistance to antibacterial effect of Cefixim and this indicator that no difference in quality of antibiotics is created by the great difference in the price.

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