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RESEARCH ARTICLE

Evaluation of antibacterial activities of three commonly used antibiotics produced by different manufactures on female urinary tract infection uropathogens in Kalar city.

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ABSTRACT

Health professional staff often claims information about trying to differentiate the used antibiotics based on the manufacturers that produce the drug, which may lead to a differentiation in the prescribing of the antibiotics by a physician**.** Numerous antibiotics produced by different manufactures, under different brands names are available in pharmacies for urinary tract infection (UTI) treatment; this study proceeds to find out and evaluates antibacterial activities of three most used antibiotics, produced by different antibiotic producers on uropathogens in Kalar city. Kirby–Bauer disk diffusion method is employed to assess antibacterial effectiveness of Amikacin (Ak), Levoflaxocilin (Lv) and Nitrofuratoin (Nr) against reference strains of *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus saprophyticus* and clinically isolated uropathogens (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus saprophyticus*, *Proteus vulgaris*, and *Klebsiella pneumoniae)*. Inhibition zones (IZ) were determined in millimeter unit to show the activity of the antibiotics. It has been found that the activity of all brands on sensitive bacterial strains were in the preferred range and surpassed the threshold of (IZ) determined by Clinical Laboratories Standards Institute (CLSI) guide. The lack of significant differences among most tested brands for each antibiotic, support this idea.

Keywords: Amikacin, Levofloxacin, Nitrofurantoin, manufactures, Uropathogens

INTRODUCTION

Since the discovery of first antibiotic in the early 20th century, mankind has been in a continuous race to discover new antibiotics to treat and control the microbial infectious diseases, so the pharmaceutical industries developed and produced many antibiotics that save the lives of millions of people from various diseases and help many people who suffer from illness to recover, that made the using of antibiotics to be increasing worldwide (van de Sande-Bruinsma et al., 2008).Since urinary tract infection is one of the most common diseases, especially among women, and it is caused by various species of bacteria(Johnson & Russo, 2018), it is logically to be one of the diseases requiring more antibiotics to achieve the best recovery. Empirical use of different classes of antibiotics to treat UTI and other infectious diseases is one of the major healthcare issues that resulted in treatment failure which necessitated the trying of other types and other brands of antibiotic especially in developing countries (van de Sande-Bruinsma et al., 2008). The quality of medicines play an important role in successful treatment, low-quality antibiotics contribute to the development of antibiotic resistance, making it extremely difficult to treat the disease with available antibiotics (Chokshi et al., 2019). The laboratory testing of antibiotic susceptibility have a direct impact on patient treatment and data generated from an antibiotic susceptibility test serves as a guideline for preventing microbial resistance during deciding therapy and still the method of choice for the clinical microbiologists for the in vitro antimicrobial susceptibility testing is the disc diffusion method (Bauer et al., 1966). The Kirby-Bauer technique for disk susceptibility testing has been recommended by the CLSI, which is approved by the US FDA and is also recommended by the WHO (Humphries et al., 2021). Acceptance of the in vitro disk-susceptibility method has been aided by its simplicity, rapidity and standardization of the technique also controls variation in results. The interpretation is based on comparison of inhibition zones with published criteria for zone diameters (Bauer et al., 1966).

Antibiotics used to treat UTIs are typically capable of reaching high urinary concentrations, indicating that they are clinically effective (Novelli & Rosi, 2017). Fluoroquinolones have played an important role in the treatment of these infections because they have a broad spectrum of activity against both gram-positive and gram-negative bacteria (Cruciani & Bassetti, 1994), so they are

the most common antimicrobial agents used globally in treating UTIs (Tan et al., 2017). Levofloxacin is widely used in clinical practice because of its established efficacy and safety (Ball, 2003). Levofloxacin is a bactericidal antibiotic that works by inhibiting bacterial DNA replication through inhibiting two important bacterial enzymes: DNA gyrase and topoisomerase IV (Fàbrega, et al., 2009).

Aminoglycosides are high potent, broad-spectrum antibiotics widely used for the treatment of life-threating infections, including the urinary tract infections (Ferrara & Kong, 2008). Amikacin a broad-spectrum aminoglycoside is mainly used in Asian and certain European countries (Maraki et al., 2012). Amikacin binds to bacterial 30S ribosomal subunits and interferes with mRNA binding and tRNA acceptor sites, interfering with bacterial growth. This leads to disruption of normal protein synthesis and production of non-functional or toxic peptides (Omri & Ravaoarinoro, 1996).

Nitrofurantoin is an antibiotic belongs to Macrobid antibiotic group that is used for treating urinary tract infections caused by different types of bacteria. It is effective against E. *coli*, *Klebsiella*, and *Staphylococcus* sp.(Komp Lindgren et al., 2015) It works by damaging bacterial DNA, since its reduced form is highly reactive. Nitrofurantoin interferes with the production of bacterial proteins, DNA, and cell walls (McOsker & Fitzpatrick, 1994).

This study aims to examine the activity of different brands of the above mentioned three antibiotics that are available at the drug stores in Kalar City against distinct bacterial species causing treat urinary tract.

MATERIALS AND METHODS

The study involved the purchase of three major antibiotics which are commonly used as well-known antibiotics to treat urinary tract infections; each one of them was obtained with five different commercial brands from different manufactures countries and standard discs for each antibiotic from oxoid UK. A total of fifteen different brands (arranged A-F) of the three major antibiotics were collected from different drugstores in the city of Kalar. The antibiotics were evaluated for activity based on mean inhibition zone diameter, which is a measure of the accuracy and range of zone diameters against both standard ATCC strains and clinical isolates of uropathogenic bacteria. The study is done in May-November 2021.

Sampling

A sample size (quantity amount) of 15 different brands of antibiotics (Vials, tablets, and/or capsules) of Amikacin, Levofloxacin and Nitrofurantoin were targeted based on the assumption: at least 5 different brands of antibiotics were available in the market for each of the three antibiotics (Table). The antibiotics were assayed separately to test the activity and compare among the manufacturers.

Table: List of the names of the antibiotics and some of their profile.

N	Type	State	Dosage form	Batch number
1	Amikacin	Egypt	Vial	1808158
2		Malaysia	Vial	180215E
3		India	Vial	KD/2177-A
4		Spain	Vial	P1X71
5		Iran	Vial	0020219
6	Levo-floxacin	Iraq	Tablet	BL2012
7		Australia	Tablet	8088609
8		India	Tablet	LB8002
9		Turkey	Tablet	09300376
10		UK	Tablet	17X1209
11	Nitro-furantoin	Turkey	Tablet	8811034
12		Switzerland	Capsule	1950210
13		Belarus	Tablet	3670518
14		Turkey	Capsule	8213031
15		Greece	Tablet	LOT181318

Biological and chemical materials

Reference strains of three bacteria *Staphylococcus saprophyticus* (ATCC15305), *Pseudomonas aeruginosa* (ATCC27853), *Escherichia coli* (ATCC25922) provided by Media Medical Center in Erbil, Kurdistan region, Iraq and five clinically isolated bacteria from patients with confirmed UTI: *Staphylococcus saprophyticus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis, Klebsiella pneumoniae* were obtained and re-identified by VITEK ® 2 compact systems. Three antibiotics: Amikacin, Levofloxacin and Nitrofuratoin, each from five different brands that are available in the pharmacies (Table). Antibiotics discs of identical potency, from Oxoid, UK were purchased and used as positive controls.

Preparation of the antibiotics

The antibiotics were diluted by suitable solvents (distill or buffer phosphate water) to obtain concentration equal to their standard discs (Amikacin (AK; 30µg); Levofloxacin (LV; 5µg); Nitrofuratoin (NR; 100µg).

Antibacterial assays

The antibacterial activities of the different antibiotic samples were evaluated against the reference and clinically isolated strains of bacteria using the Kirby–Bauer disk diffusion method. Five discrete colonies from each of the reference strains and clinically isolated bacteria were separately inoculated into 5 mL of culture broth and incubated at 37°C for 4–6 hours. The resultant bacterial suspensions were adjusted using sterile culture broth to match a standard turbidity (McFarland; 0.5 M) prior to subjecting them to susceptibility profiling on Mueller–Hinton agar plates (Difco™; BD, Franklin Lakes, NJ, USA) as per the CLSI (Humphries et al., 2021). Each standard/control antibiotic disc was placed in the center of the same agar plate with a corresponding test antibiotic that put in wells with fit diameter of the standard disc as described by (Magaldi et al., 2004). The prepared antibiotic solution of each antibiotic (as described previously) was placed aseptically in well onto the agar plate using sterile micropipette. The wells were made 34 mm apart andat least 15 mm from the edge of the Petri dish. The plates were incubated at 35°C for 24 hours. Each sample of antibiotic was tested twice in triplicate. Results were expressed as the diameter of IZ in millimeter unit as previously described.

Ethical issues and definition of terms

The College Ethical Committee approved this study. For legal and commercial purposes, the antibiotic manufacturers were not revealed, and only the antibiotic sample batch numbers and their country of origin are given.

Statistical analysis

The data are processed using one way analysis of variance (ANOVA), Dunkan's multiple range test with confidence intervals of 0.05 and expressed as mean± standard deviation (SD).

RESULTS

The results of this study were supported by the repetitive standards procedure of the three major antibiotics with five different brands and three standard discs one for each antibiotic to obtain the final results which were conducted from a summation of 288 sample replications of the antibiotic sensitivity test.

Antibacterial activity of Amikacin against the reference bacterial strain

According to CLSI guide the range of (19-26) mm IZ is dependable for the activity of amikacin (AK) against E. *coli* ATCC25922. The means of IZ ± SD for all brands were:-A (22.3±1.2), B (21.6±1.2), C (20.8±0.9) D (21±0.8), E (22±1.2) and F (20.8± 0.9). The results showed no significant differences among all brands (P=0.1), as well as no significant differences were found between B, D, E brands and standard A disc (P=0.06), while C and F brands showed low significant (P= 0.045) differences. The (IZ ± SD) for all brands for *P. aeruginosa* among brands were in the range (18-26) mm determined by CLSI for the activity of (AK) against this strain and were as follow: - A (26.8±1.7), B (24.2±0.8), C (22.6±3.9), D (22.5±1), E (24.5±2.1) and F (22.6± 1.9) mm. No significant differences were obtained among all brands (P=0.16), also no significant differences were obtained between E and standard A while other brands were significantly (P= 0.03) different. Meanwhile the CLSI determined the threshold as (17) mm for *Staphylococcus* spp. The mean ±SD of IZ for all brands were: - A (29.6±0.8), B (26.5 ±1.5), C (27 ±2), D (26.1±1.9), E (28.1±1.8) and F (25.3±1.8). No significant differences (P=0.13) among F, D, B, C brands, no significant (P=0.076) differences among D, B, C, E, brands, no significant difference (P=0.144) between brands E and standard A disc while B, C, D, F brands showed low significant (P=0.04) differences [Figure 1].

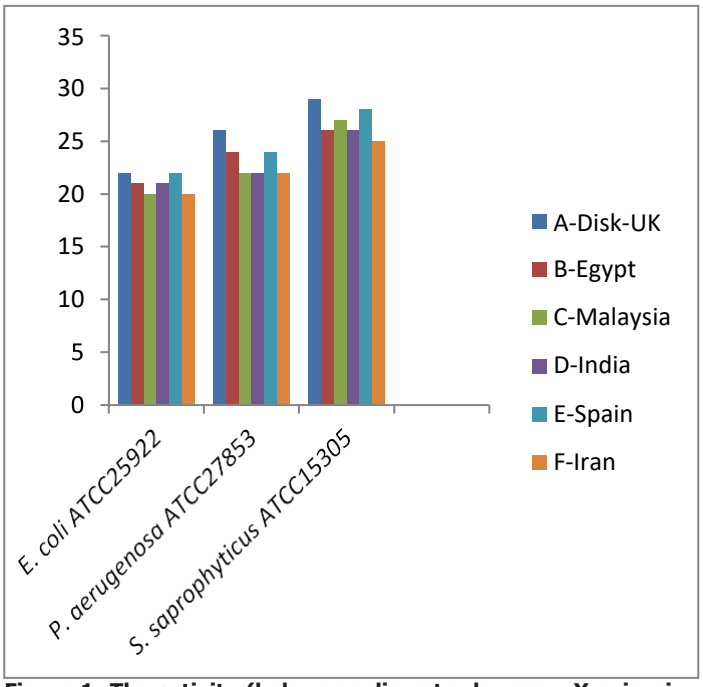

Figure 1: The activity (halo zone diameter by mm – Y axis, six replicates) of standard disc and five different Amikacin sulfate brands against different ATCC bacterial strains (X-axis).

Antibacterial activity of Amikacin against the clinically isolated bacterial strains

Based on CLSI threshold (IZ ≥17 mm) is determined for *E .coli*, the (IZ ±SD) for all brands: - A (21.6±1.2), B (20.5 ± 1.6), C (20.5±1.6), D (19.5 ±1.3), E (20 ± 1.7), F (20.5± 1) were in the range. No significant differences (P= 0.3) were found among all brands, no significant differences (P=0.08) among B, C, E, F and standard A disc, while D significantly differenced with standard A disc. Whereas the CLSI threshold is (IZ ≥17) for *Klebsiella pneumoniae*, the (IZ ±SD) of all brands were: - A (21.3±1.8), B (19.8±0.7), C (19.8±1.4), D (19.1±1.1), E (20 ±1.4), and F (19.3 ±1.3). No significant differences (P=0.3) among all brands, no significant differences (P=0.9) among B, C, E and standard A disc, while D and F showed significant differences (P<0.05) with standard A disc. At the time that CLSI threshold is (IZ ≥17) for *Proteus mirabilis*, the (IZ ±SD) of all brands were less than (17mm) as: - A (10.3±1), B (9.1 ±1.1), C (9.3 ±1), D (8.5 ±1.3), E (9.8 ±1.1), F (8.5 ±1.3). No significant differences (P=0.08) among all brands, no significant differences (P=0.1) among B, C, E and standard A disc, while D and F significantly differenced with standard A disc. The CLSI threshold is (IZ ≥17) for *Pseudomonas aeruginosa* and the (IZ ±SD) of all brands were: - A (21.8±1.4), B (19.6±0.8), C (19.1±0.75), D (19.5±1), E (20.3 ±1.5), and F (19.1 ±1). No significant differences among all brands, while all were significantly differenced with standard A disc. The CLSI threshold is (IZ ≥17) for *Staphylococcus saprophyticus*, the (IZ ±SD) of all brands were:- A (32 ±1.2), B (30.8 ±0.9), C (31 ±0.9), D (31.1 ±1.1)) E (31.5 ±1.3), F (30.8 ±0.98). No significant differences (P=0.1) among all brands, no significant differences (P=0.1) among C, D, E and standard A disc, while D and F showed significant differences with standard A disc [Figure2].

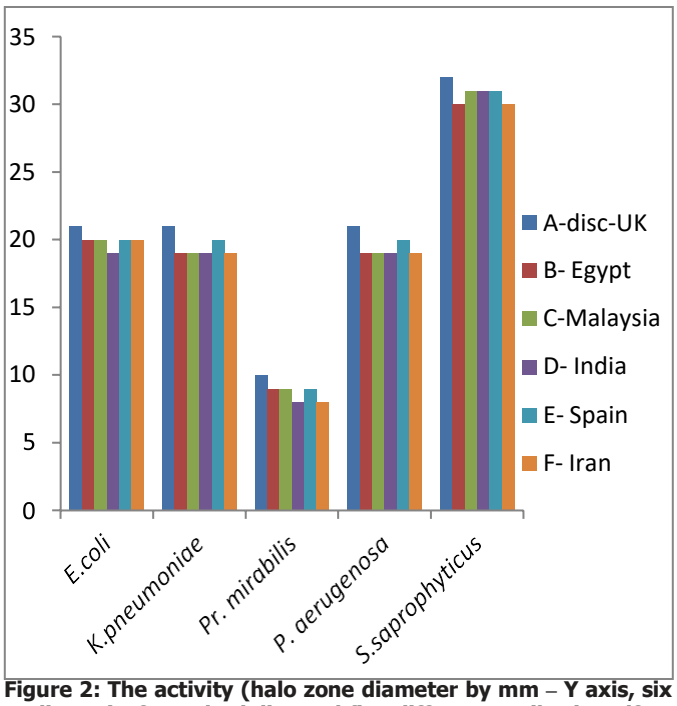

Figure 2: The activity (halo zone diameter by mm – Y axis, six replicates) of standard disc and five different Amikacin sulfate brands against different clinically isolated bacterial strains (X-axis).

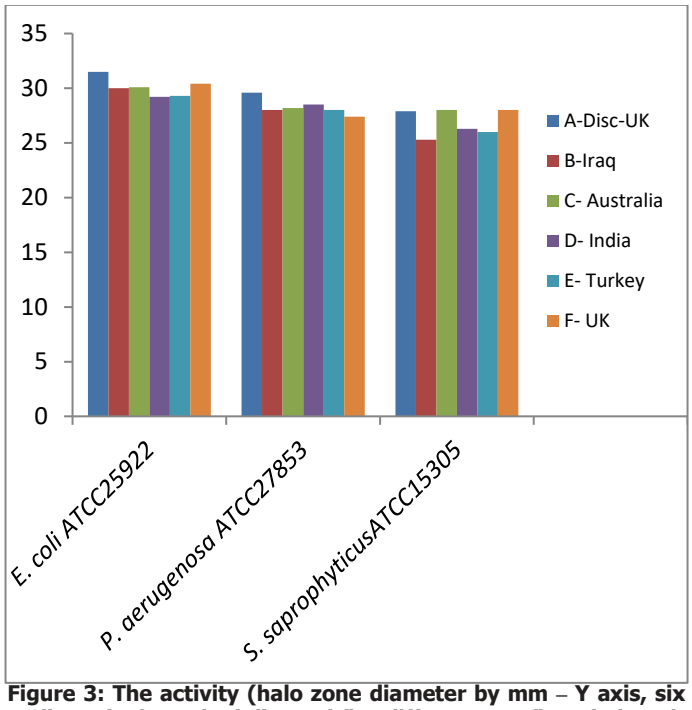

Figure 3: The activity (halo zone diameter by mm – Y axis, six replicates) of standard disc and five different Levofloxacin brands against different reference bacterial strains (X-axis).

Antibacterial activity of Levofloxacin against the reference bacterial strains

In the same manner that performed to the previous antibiotic activities and within the same procedures, the results for levofloxacin sorted below:

The established CLSI range is (29-37)mm for *E.coli ATCC25922*, the IZ (±SD) of all brands: - A (34.3±1.3), B (32.6±1.8), C (33.1±1.7), D (31.1±1.4), E (31.5± 2) and F (32.3 ±2.3) . No significant differences (P=0.1) among all brands, no signiicant differences (P=0.09) between(F,B,C) and (A) the standard disc, while D and E significantly differenced with the standard A disc.The CLSI range is (19-26)mm for *Pseudomonas aeruginosa ATCC2785*, the (IZ±SD) of all brands were: - A (31.6± 1.6), B (31±1.2), C (29.6± 1), D (29.3±0.8), E (29±1.2) and F (29±1.1). No significant differences (P=0.396) among E, F, D, C brands and no significant differences (P=0.069) between B & C. As B non significantly (P=0.35) differenced with A standard disc, the others brands significantly differenced with the standard A disc.The CLSI range is also (19-26)mm for *Staphylococcus saprophyticus ATCC15305*, while the (IZ±SD) of all brands were: - A (27.6± 1.3), B (26.8±1.1), C (28±0.8), D (26.8±1.1), E (26.5±1) and F (27.1±1.1). No significant differences (P=0.1) among all brands, no signiicant differences (P=0.1) between(D,F,B,C) and A standard disc, while E significantly (P<0.05) diffrenced [Figure 3].

Antibacterial activity of Levofloxacin against the clinically isolated bacterial strains

The CLSI threshold is (IZ ≥17mm) for *E. coli*, the (IZ ±SD) of all brands were: -A (31.2±1.2), B (30.5±1.5), C (30.3±1.3), D (29±0.9), E (29.6±1.2) & F (30.1±0.9). No significant differences (P=0.06) among all brands, no significant differences (P=0.1) between (E, F, B, C) and A standard disc, while D significantly differenced. The CLSI threshold is also (IZ≥17mm) for *Klebsiella pneumoniae*, while the IZ (±SD) for all brands were: - A/29(±0.9), B/ 28.3(±1.2), C/ 28(±1.4), D/ 28(±1), E/ 28.8(±1.1) & F/27.6(±1.2). No significant differences (P=0.09) among all brands, no significant differences (P=0.09) between all brands and standard A disc. CLSI threshold is also (IZ≥17mm) for *Proteus mirabilis*, while the (IZ ±SD) obtained for all brands were: -A (31.5±1.5), B (31±1.2), C (30 ±0.9), D (31±0.9).E/30.8(±1) & F (31.5±1.3). No significant differences (P=0.06) among all brands, no significant differences (P=0.06) between all brands and A standard disc. CLSI threshold is (IZ≥19mm) for *Pseudomonas aeruginosa*, the (IZ ±SD) results for all brands were: -A (31.8±1.1), B (31.5±1.3), C (31.3±1.5), D (31±1.1), E (31.1±1.1) & F (30.5±1). No significant differences (P=0.1) among all brands, no significant differences (P=0.1) between all brands and A standard disc. At the time that the CLSI threshold is (IZ≥17mm) for *Staphylococcus saprophyticus*, the (IZ ±SD) data for all brands were: - A (32.6±1.2), B (31.6±1.9), C (31.1±1.1), D (30.5±1.6), E (31.1±1.1) and F (30.8±0.7). No significant differences (P=0.1) among all brands, no significant differences (P=0.1) between (B.C, E) & A standard disc, while D and F significantly differenced with standard A disc [Figure 4].

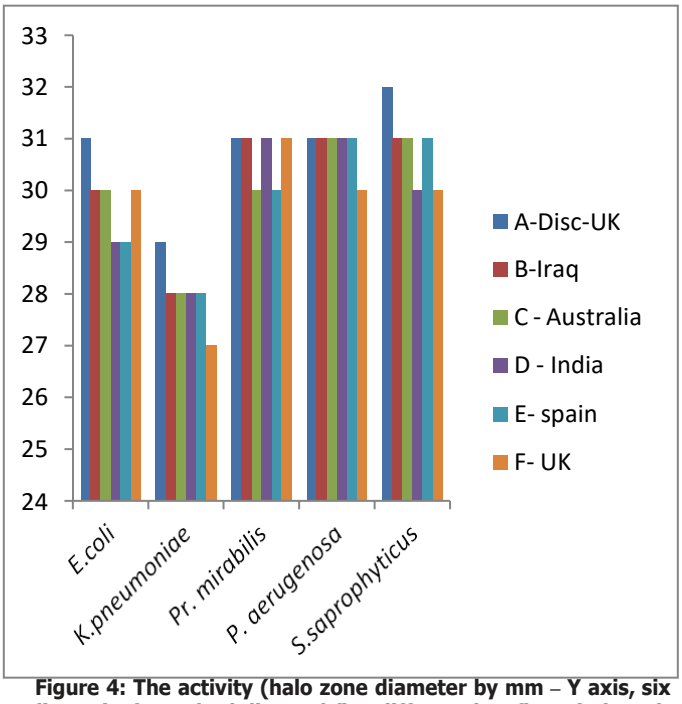

Figure 4: The activity (halo zone diameter by mm – Y axis, six replicates) of standard disc and five different levofloxacin brands against different clinically isolated bacterial strains (X-axis).

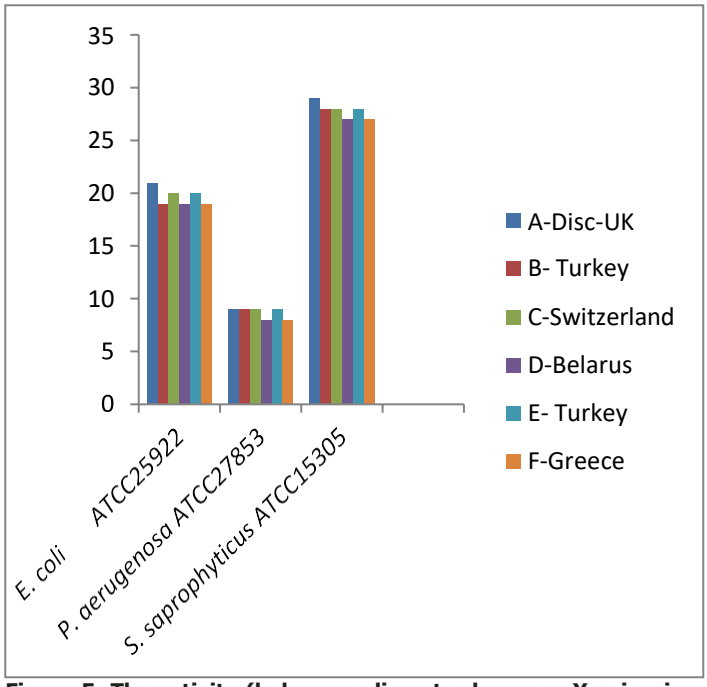

Figure 5: The activity (halo zone diameter by mm – Y axis, six replicates) of standard disc and five different nitrofuratoin brands against different reference bacterial strains (X-axis).

Antibacterial activity of Nitrofurnatoin against the reference bacterial strains

CLSI range is (20-25) mm for *E. coli ATCC25922*, the (IZ ±SD) for all brands were: - A (21.1±1.4), B (19.3±0.8), C (20.5±1.3),D (19.8±1.1), E (20.6±1.2), and F (19.3±0.8). No significant differences (P=0.087) among all brands, no significant differences (0.08) among (C, D, E) & standard A disc, while B and F significantly differenced (P<0.05) with standard A disc. At the time that the CLSI threshold is (14) mm for *Pseudomonas aeruginosa ATCC27853*, the (IZ ±SD) of all brands were lower than this level, so all were out of activity as follow: - A (9.6±1.2), B (9.3±0.8), C (9.1±1.1), D (8.6 ±1.2), C (9±1.2), F (86±1.2). No significant differences (P=0.19) among all brands, no significant differences (0.19) between all brands and A standard disc. CLSI threshold is (19) mm for *Staphylococcus saprophyticus ATCC15305* and the IZ (±SD) of all brands were: -A (29.3±1.6), B (28.3±1.6), C (28.3±1.3), D (27.5±1.6), E (28.5±1.3) & F (27.8±1). No significant differences (P=0.06) among all brands, no significant differences (0.06) between all brands and standard A disc [Figure 5].

Antibacterial activity of Nitrofuratoin against the clinically isolated bacterial strains

CLSI threshold is (IZ≥17) mm for *E. coli*, the (IZ ±SD) of all brands: -A (19±0.89), B (18±0.89), C (18.1±0.75), D (17.5±1.37), E (17.6±0.8) & F (17±0.89). No significant differences (P=0.68) among all brands, no significant differences (P=0.098) between (B, C) brands and standard A disc. The CLSI threshold is (IZ≥14) mm for *Klebsiella pneumoniae*, while the (IZ ±SD) of all brands were out of the range: - A (9.3±1), B (8.5 ±1), C (8.3±1.2), D (8.5±1) E (7.8±1.7) & F (8.1±1.1). No significant differences (P=0.07) among all brands, no significant differences (P=0.07) between all brands and standard A disc. The CLSI threshold is (IZ ≥17) mm for *Proteus mirabilis*, while the (IZ ±SD) of all brands again were less than this point: - A (10.3±1.5), B (10±1.6), C (10.1±1.6), D (9.1±1.7), E (8.8±1.47) & F (8.6±1.6). No significant differences (P=0.123) among all brands, no significant differences (P=0.123) between all brands and standard A disc. The CLSI threshold is (IZ ≥14) mm for *Pseudomonas aeruginosa*, but the (IZ ±SD) of any brand was not passed this point and were: A (10.1±1.1), B (9±0.89), C (9±1.2), D (8.8±1.9, E (9 ±1.7) & F (9±1.4). No significant differences (P=0.173) among (B, D, F), no significant differences (P= 0.173) among all brands and standard A disc. The CLSI threshold is (IZ ≥17) mm for *Staphylococcus saprophyticus*, the (IZ ±SD) of all brands were: - A (25.5±1.6), B (23.1±2.1) C (24±1.4), D (20.8±1.9), E (24(±2.3), F (21.6±1.6). No significant differences (P=0.051) among (B, D, F), no significant differences (P= 0.57) among (F, B, C, E), no significant differences (0.057) among (B, C, E) and standard A disc, while D and F significantly (P<0.05) differed with A standard disc [Figure 6].

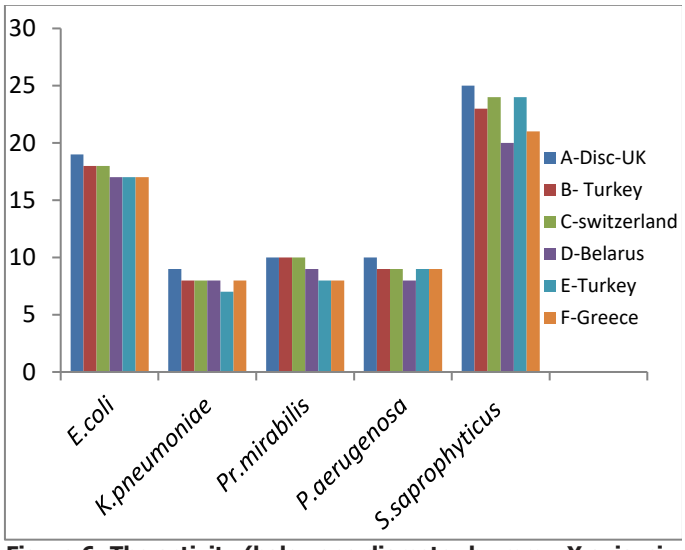

Figure 6: The activity (halo zone diameter by mm – Y axis, six replicates) of standard disc and five different nitrofurantoin brands against different clinically isolated bacterial strains (X-axis).

DISCUSSION

Various brands of the same antibiotic are available at health markets for treating urinary tract infection. It is well known that amikacin is one of the main broad spectrum antibiotics wildly used to treat UTI (Maraki et al., 2012). The results of this study showed that all brands of amikacin tested are considered effective according to the CLIS guide against all reference bacterial strains and all clinically isolated bacteria except *Pr. mirabilis*, which was resistant. No significant differences (P> 0.05) among all brands activity against all tested species (except brand (E) against *S. saprophyticus* ATCC15305) confirm these results. Amikacin was active against *E. coli*, a study performed in china on E. coli (n=811) and *K. pneumoniae* (n=835) found that 96% of all isolates tested were susceptible to amikacin (Kutiet al., 2018).

Amikacin worked well against P. *aeruginosa*, a study conducted in China on 392 bacterial isolates of E. coli (n=151), *K. pneumoniae* (n=129), *P.aeruginosa* (n=112), amikacin showed better susceptibility rates to most antibiotics tested (Sutherland et al., 2016). Pr. *mirabilis* isolates were resistant to all brands of amikacin these results are supported by a study of 120 urine samples taken in Erbil hospitals/Iraq from individuals infected with UTIs revealed that *Proteus* sp. was resistant to all tested antibiotics including amikacin (Alshwaikh et al., 2014). Both reference and clinically isolated *S. saprophuticus* strains were sensitive to all brands of amikacin, a study done at Dhaka National Medical College &Hospital, Bangladesh on 292 bacterial isolates from patients suspected to be infected with UTI, 16 isolate of *S. saprophyticus* were sensitive (81.86%) to Amikacin (Islam et al., 2019) and another study on ninety one (91) clinical urine samples done at Bauchi metropolis/ Nigeria showed that most (73.3%) of S. *saprophyticus* isolates were highly sensitive to Amikacin (Iliyasu et al., 2015) that support the current study results. The activity of amikacin is associated with its ability to disrupt the process of protein synthesis through binding to bacterial 30S ribosomal subunits and interfering with mRNA binding and tRNA acceptor sites (Omri & Ravaoarinoro, 1996).

On the other hand, levofloxacin has also been used due to its activity against many pathogenic bacteria that cause urinary tract infections (Mascellino et al., 1998). It is widely used in clinical practice because of its established efficacy and safety (Ball, 2003). The results of the current study showed that all brands of levofloxacin tested were effective against all reference and clinically isolated bacteria depending on CLIS guide. No significant differences (P> 0.05) among all brands activity against all tested species (except brands (B&C) against *P. aeruginosa* ATCC278530) support the previous conclusion. Many studies were in line with these results, a study on 200 clinical isolates at 'L. Sacco' Teaching Hospital of Milan /Italy, showed that all (25) *E. coli* isolates were susceptible to levofloxacin (Drago et al., 2001), another study done on 200 clinical isolates, including the species *E. coli*, *K. pneumoniae*, *Pr. mirabilis*, concluded that all isolates were susceptible to levofloxacin (Bonfiglio, 2001), next study on 100 clinical samples revealed that the susceptibility of *S. saprophyticus* isolates for Levofloxacin was 83.3% (Imarhobobhor & Isibor, 2017). Levofloxacin works by inhibiting bacterial DNA replication through inhibiting DNA gyrase and topoisomerase IV enzymes, the two important enzymes for bacterial replication (Fàbrega, et al., 2009).

Nitrofurantoin has also been prescribed as an effective antibiotic for urinary tract infections, the results of the current study revealed that all tested brands were active against the reference strains and clinically isolated *E .coli* and S. *saprophyticus*, while it was not active against the reference strains and clinically isolate of *P.aeruginosa*, *K.pneumoniae* and *Pr.mirabilis* according to CLIS guide, however statistically no significant differences (P>0,05)were found among all brands activity against all tested species (except brands (C & D) against *P. aeruginosa* & *S. saprophyticus*). Nitrofurantoin is bactericidal to a mean of 95% of E. *coli* UTIs (Brumfitt & Hamilton-Miller, 1998) and it is highly effective against *S. saprophyticus* isolates (Komp Lindgren et al., 2015) that made the resistance among E. coli to be lowest for nitrofurantoin (less than 1%) (Edlin et al., 2013; Kashanian et al., 2008) A study done on 68 bacteriologically proven simple UTI patients, concluded that *K. pneumoniae* isolates were highly resistant to nitrofurantoin (Rizwan et al., 2018), another study done on total of 1723 urine culture sensitivity reports of patients who were suspected to be having UTI, from July 2016 to Feb 2017 in a tertiary care hospital of Jharkhand, India concluded that all isolates of *p. aeruginosa* were absolutely resistant to nitrofurantoin and another study done in the microbiology section of the Central Laboratory of Tabriz University of Medical Sciences on 5136 outpatients suspected of having a UTI, also reported that all (100%) *p. aeruginosa* isolates were highly resistant to nitrofurantoin (Arabi et al.,

2008; Kumar et al., 2017). Nitrofurantoin works by damaging bacterial DNA through interfering with the production of bacterial proteins, DNA, and cell walls of sensitive bacteria (McOsker & Fitzpatrick, 1994), while *Klebsiella pneumoniae*, *Proteus mirabilis* and *pseudomonas aeruginosa* are genetically resistant to nitrofurantoin (Brumfitt & Hamilton-Miller, 1998; Mirzaei et al., 2021).

The finding of significant differences ($P<0.05$) between antibiotic brands and their standard discs may in most cases be due to the difference in physical nature, since the discs are dry while the antibiotics are liquid, resulting in scattering differences of spreading of the antibiotics in the culture media.

CONCLUSIONS

According to the CLSI guide, the brands of each the three tested antibiotics were demonstrated accepted antibacterial activities against the sensitive tested uropathogns to these antibiotics, and generally, no significant differences were noticed among the brands of each antibiotic whether uropathogens were sensitive or resistant that negates the differentiation among the antibiotic brands, which may be reflected even on their prices in drug stores.

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