Egyptian Journal of Veterinary Sciences

https://ejvs.journals.ekb.eg/

Role of Plantaricin in Treatment of UTIs in Female Rats

Aula Hassoon Obaid* and Ali H. Saliem

College of Veterinary Medicine, University of Baghdad, Iraq.

Abstract

THE purpose of the present research is to investigation of plantaricin against urinary tract infection that induced by *E.coli O157H7* in female rats , which consisted of two steps; the first included isolation and identification of *E.coli O157 H7* by using biochemical tests and VITEK II system, while the second step is studying the therapeutic activity of plantaricin (which isolate from Lactobacillus plantarum and identified genetically by PCR) against the UTIs that induced experimentally by *E.coli O157:H7* in 32 female rats (which are divided into four equal groups), and comparison of these effects with ciprofloxacin. The results of this research showed that plantaricin has a clear therapeutic effect in the treatment of UTIs through its effect on body weight and improved clinical markers as well as urine bacterial count and level of creatinine in serum of female rats that compared to animals, were more heavily infected with *E. coli O 157;H7* that have been infected with *E.coli O157:H7* and not been treated or with animals that treated with ciprofloxacin. This antibacterial activity that characterizes the plantaricin due to natural and safe antimicrobial effects against pathogenic *E. coli O157:H7.*

Keywords: Therapeutic effect, plantaricin, UTIs, *O157:H7*, rats, creatinine.

Introduction

In clinical practice across the world, urinary tract infections (UTIs) are the most prevalent illnesses. Despite several attempts, UTIs continue to be serious health problems that afflict millions of people annually around the world, resulting in significant incidence and huge healthcare costs. [1].It is also a common and complicated infection among human or animals. Global estimates revealed that both females and male experienced no less than one UTI episode cases [2-3].

Typically, there are two classifications of UTIs. Acute cystitis, categorized as the first, affects the lower urinary tract. The second disorder is acute pyelonephritis, which impacts the upper urinary systematic bacteriuria, which refers to the presence of specific bacteria levels in the urine but no obvious signs [4-5], and high bladder bacterial burdens [6]. *Escherichia coli*, Proteus, and Staphylococcus organisms account for 90% of the initial clinical UTIs and 70% of recurrent infections that are caused by infections caused by bacteria, which are also the most prevalent source of UTI [7]. *Escherichia coli* are a gram negative bacterium which is responsible for the frequency and severity of infections [8-9]. Despite Shiga toxin-producing *Escherichia coli* (STEC) infections accounting for the majority of cases, hemolytic uremic syndrome (HUS) are one of the most frequent causes of acute renal failure. O157 is still the most common STEC genotype [10].The progressing with uses of ciprofloxacin lead to side effects, as well as hyper or hypoglycemia, photosensitivity, and tendinitis, are among the significant adverse effects of ciprofloxacin [11]. Probiotics are types of microbes that are alive that, when given in sufficient doses, have positive effects on the well-being of the recipient [12]. *Lactobacillus plantarum* produces the new bacteriocin known as plantaricin which usually included in both class I and II. Class I includes bacteriocins which named plantaricin [13]. In the future, plantricin may replace conventional antibiotics as an efficient drug for the avoidance and management of infectious infections [14].

The aim of current study is to evaluate the therapeutic effect of plantaricin combined with

*Corresponding author: Aula Obaid, E-mail: ula.hassoun1106h@covm.uobaghdad.edu.iq, Tel.: 009647715818805
(Received 30/12/2023, accepted 08/02/2024)
DOI: 10.21608/EJVS.2024.259437.1756

ciprofloxacin against urinary tract infection by *E.coli O157:H7.*

Material and Methods

Source of *E.coli O 157:H7*

The strain of *E. coli O157*: H7 bacteria were obtained from AL-Karama hospital in Wasit Governorate, from female suffering from acute UTIs,this bacteria identified by Vetik IIsystem and biochemical characteristics according to [15].

Extraction of plantaricin from *Lactobacillus plantarum*

Plantaricin was produced from *lactobacillus plantarum ,* the isolate has been grown from a local sample (sourdough sample) by using a growth medium called MRS broth [16].The plantaricin gene was identified by PCR [17].

Animals

Thirty two (32) female Wister albino rats were three to four months old and 176 to 250 g body weight; have been kept in plastic containers measuring 20 x 50 x 75 cm and placed in a dedicated housing area at the College of Veterinary medicine University of Baghdad for two weeks in order to acclimate. Both tap water and the typical rat food (commercial feed pellets) were readily presented. Habitat circumstances were kept at 20-25 ^{o}C in air-conditioned rooms. The air in the rooms was regularly replaced using ventilation vacuums. Every day, the containers' litter was replaced.

Inducing of Infection (UTI)

The bacteria utilized *E. coli O157:H7* suspension (2.6 x 10^{6}) CFU/ml is the source of the illness (acute UTI). The inoculations were prepared and standardized using a pour plate approach and repeated one-tenth dilutions. The rats received 0.1 ml of each dilution intra urethral and the animals were monitored for signs of UTI. The solution that caused the rat's infection, as shown by the symptoms, has been used as the rats' infectivity dose during the whole illness [15]. 24-hour culture over night at 37°C in 0.1-ml dilutions of brain-heart infusion broth has been given with a canula (gauge 24G) to each rat of the infected groups.

Experimental Design:

Thirty-two female rats were divided randomly into four groups (8 rats in each group).

1. Group A (Negative control): 8 normal female rats not infected with *E. coli O157 H7* , given only distilled water orally.

2. Group B (Positive control): 8 female rats infected with *E.coli O157 H7* and not treated.

3. Group C: 8 female rats infected with *E. coli* O157 H7 were given ciprofloxacin orally twice a day at a dose of 14.28 mg/kg [18].

4. Group D: 8 female rats infected with *E. coli* O157:H7 were given plantaricin orally (0.5g/kg) twice daily [19].

Body Weight Changes

Animals' weights were recorded before an infection was induced, throughout the first week of treatment, and after seven and 14 days of therapy.

Clinical Signs:

Clinical signs, urine color, unusual frequency in urination, cloudy urine or foul smelling, changes in behavior, activity, food and water conception and death rate in animal groups were continuously recorded during the period of the experiment.

Blood Serum Samples

Blood samples collected prior to infection, seven days after infection, and fourteen days following treatment. All female rats were anesthetized with chloroform. Direct cardiac puncture of rats was used to obtain blood samples, which then sera were placed in dry, clean, and sterile tubes (gel tubes), allowed to clot for a short period of time 15 minutes of centrifuging at 4000 rpm at room temperature to separate the clear sera, and this were then placed in Eppendorf tubes by micropipette and kept in a deep freezer at (-80^{o}C) till performing the biochemical analysis [20].

Determination of serum creatinine concentration (mg/dl)

This test was made by using creatinine kit (Biosystem company, Spain) to determine the serum creatinine concentration following a 14-day therapy period and a 7-day infection-inducing period.

Urine bacterial count

Urine sample were collected in a sterile glass tube After a week of infection induction and 14 days of therapy, there was an increase in the amount of *E. coli* O157:H7 found in urine samples. 0.1 ml of urine sample was suspended to 0.9 ml of diluents that containing 0.1% of peptone water [21,22]. The bacterial counting (CFU/ ml) was calculated by using the following formula [15].

$$\textbf{Number of bacteria/ml} = \frac{\textbf{No.of colonies (CFU)}}{\textbf{dilution factor X amount plated}}$$

Statistical analysis

Statistical Analysis System- SAS [23] program was utilized, a significant comparison of means was made using the difference that was least significant (LSD) test (ANOVA).

Result and Discussions

Biochemical identification of *E. coli* O157:H7

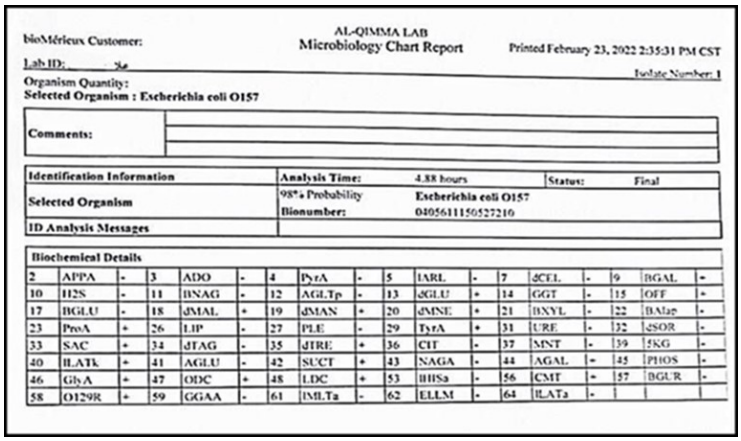
The result of biochemical tests are explained in the table (1) and these results were in agreement with [24].

TABLE 1.Biochemical tests for identification of *E. coli* O157:H7. Vitek II System

NO.	Biochemical tests	Results
1	Catalase	+
2	Oxides	-
3	Indole	+
4	Methyl red	+
5	Voges-Proskauer	-
6	Citrate utilization	-
7	KIA	**A/A**
8	Ureas	-
9	Motility	+
10	Gelatinase	-

(+) Positive result, (-) negative result, (KIA) Kliger Iron Agar test , (A/A) Acid slant/ Acid bottom

Based on the manufacturer's technical datasheet, the isolated bacteria have achieved an excellent identification level with a probability of 98%. This was done with the automated Vitek II system by using GN-ID cards which include many biochemical tests (Fig. 1). This method is distinguished through the rapid identification of bacteria minus requiring for several mediums for culture and the decreased pollution of populations [25]. Regarding the majority of infectious disease pathogens, automated determination of bacteria in a clinical lab offers a quick and accurate diagnosis with a very desirable degree of accuracy in identification [26].On the other hand, the VITEK II system is beneficial for comparing the biochemical characteristics of *E. coli* O157:H7. [27].


bioMérieux Customer: AL-QIMMA LAB
Microbiology Chart Report
Printed February 23, 2022 2:35:31 PM CST
Lab ID: 56 Isolate Number: 1
Organism Quantity:
Selected Organism : Escherichia coli O157

Comments:

Identification Information	Analysis Time: 4.88 hours	Status: Final
Selected Organism	98% Probability	Escherichia coli O157
	Bionumber:	0405611150527210
ID Analysis Messages		

Biochemical Details

2	APPA	-	3	ADO	-	4	PyrA	-	5	IARL	-	7	dCEL	-	9	BGAL	-
10	H2S	-	11	BNAG	-	12	AGLTp	-	13	dGLU	+	14	GGT	-	15	OFF	+
17	BGLU	-	18	dMAL	+	19	dMAN	+	20	dMNE	+	21	BXYL	-	22	BAlap	-
23	ProA	+	26	LIP	-	27	PLE	-	29	TyrA	+	31	URE	-	32	dSOR	-
33	SAC	+	34	dTAG	-	35	dTRE	+	36	CIT	-	37	MNT	-	39	5KG	-
40	ILATk	+	41	AGLU	-	42	SUCT	+	43	NAGA	-	44	AGAL	-	45	PHOS	-
46	GlyA	+	47	ODC	+	48	LDC	+	53	BHSa	-	56	CMT	+	57	BGUR	-
58	O129R	+	59	GGAA	-	61	IMLTa	-	62	ELLM	-	64	ILATa	-			

Fig. 1. Identification of *E. coli* O157:H7 by Vitek II system

Extraction of plantaricin from Lactobacillus plantarum

The optimum temperature (37 ◦C) was found to be the suitable temperature for growth, while 30 ◦C and 37 ◦C were better for plantaricin production [28-17] and the identification of plantaricin was found to be as the following :

FASTA Sequence for plantaricin gene

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Query 1        AGTGCTTAAACTTGATGGCTTGAACTATCCGTGGATGAATCCTCGGACAGCGCTAATGAC  60
Subject  474   ............................................................  533

Query 61       CCAATCGGCAGGCCCAACAGCACTTTTATAATTATTCCGAGCGCCACGCGCGCTATAGGC  120
Subject  534   ..................................A.........................  593

Query  121     ATGGAAAACGCCACCTGAAATAGCATTTAATTCACGGTCACGCAAAACTAGAAAATTTTT  180
Subject 594    ............................................................  653

Query181       CATAATTGTTGATCTCCCCCAAGAAAATTAACGAATACTTTTCAAAATACCACGAATGCC  240
Subject 654    ............................................................  713
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Based on molecular weight, the discovered protein was anticipated to be plantaricin [29,30].

Induction of Urinary tract infection

Urinary tract infections were observed in rats after 24 hrs. after inoculation with the pathogenic *E coli O157:H7.*

Clinical Signs:

Prior to the infection's development, all healthy female Wistar rats displayed normal urination and light to moderately yellow urine that was normal in color. After two days of infection urine had become dark yellow, all the animals exhibited clinical signs of illness characterized by fever, dehydration, crowding, dullness, and frequent urination. However, the main clinical signs of urinary tract infection represented acute infected female rats with *E. coli O157: H7* before treatment female rats suffering from urinary disturbance [31,32].

Body Weight Changes

Differences in body mass (grams) demonstrated a relationship among sickness, kind of therapy. After 7 days of infection as shown in table, 2. Although the treatment groups' weights reduced, the control group's body weight marginally rose.

TABLE 2. Rat body weight mean± SE(g) change in several groups after infection and ciprofloxacin and plantaricin treatment during the course of experiment

Groups	Groups during different periods			
	Before infection	After 7 days of infection	After 14 days of infection	LSD value
Negative Control (A)	179.37 ±2.07 A a	180.25 ±1.48 A a	182.00 ±1.52 A a	3.28 NS
Positive Control (B)	178.87 ±1.88 A a	175.50 ±0.88 B ab	172.62 ±0.65 B b	5.16 *
Ciprofloxacin (C)	178.87 ±1.98 A a	177.25 ±1.48 AB a	181.12 ±2.01 A a	4.74 NS
Plantaricin (D)	180.12 ±1.68 A a	178.37 ±1.72 AB a	181.00 ±1.56 A a	3.78 NS
LSD value	5.353 NS	4.538 *	4.688 *	---

This shows that small characters in the same row and various capital letters in the same column are noticeably distinct. (P≤0.05).

The body's weight differences between treatment groups and the control group were not appreciably different. The weight of body was also not significantly different from control which that was agreement others [33, 29].

Urine Bacterial Count

E. coli O157:H7 colony forming unit/ml (cfu/ml) estimates for each of the four groups are displayed in table: 3. The bacteria in urine were counted using the pour plate technique, The investigated numbers showed that this method and the spread plate technique on CCA agar were both effective ways to count urine *E. coli* were simpler to use, more easy to carry out, less costly, and would produce results in only one day. Colony forming units per milliliter (CFU/ml) were used to express the amount of *E. coli* found in urine samples from the four groups. In all infected groups, a substantial rise in the *E. coli* viable count (P >0.05) was discovered. The result of bacterial count was agreement with [51]. Also, that was agreement with [34,35]they demonstrated that within 7 days of

causing urinary tract infection in female rats by injecting pathogenic *E. coli O157:H7* through inoculating the rats with (2.6 10^6) CFU/ml led to effective colonization of *E. coli O157H:7* [34].

TABLE 3. Urine Mean ± SE of Bacterial count (cfu/ml) x10^7 of rats in various groups throughout the course of the trial, were infected and given ciprofloxacin and plantaricin, respectively.

Groups	Count during different periods		LSD value
	After 7 days of infection	After 14 days of infection	
Negative Control	0.00 ±0.00	0.00 ±0.00	0.00 NS
(A)	B a	B a	
Positive Control	10735.00 ±3144.00	39462.5 ±21825.03	17602.47 *
(B)	A b	A a	
Ciprofloxacin	1986.25 ±1295.37	136.12 ±73.53	1348.92 *
(C)	B a	B b	
Plantaricin	4247.50 ±2130.0	342.50 ±127.54	1726.76 *
(D)	B a	B b	
LSD value	4526.93 *	7705.64 *	---

This shows that small characters in the same row and various capital letters in the same column are noticeably distinct. (P≤0.05).

Plantaricin could inhibit the growth of *E.coli* [29]. Also, when treated with plantaricin either ciprofloxacin showed that urine bacterial count significantly decrease (P 0.05) after seven days of therapy, After 14 days of treatment, treated group showed the bacterial count returned to normal, exactly as it had been before the infection is induced, whereas group (B) bacterial count slightly decreased (P≤0.05) when compared with seven days of treatment. This resulting in bacterial cell death and slowing the emergence of resistance [36,37]. While plantaricin dramatically decreased the viable cell count of pathogenic urine bacteria cfu/ml following treatment according to Meng *et al.* [38], pointed upon how numerous studies have focused on plantracin remarkable capacity to inhibit pathogen growth through its bactericidal activity and enable the body's immune system to combat a getting ill lacking the need of antimicrobials [39].

Serum creatinine concentration (mg/dl)

The variations in mean serum creatinine concentrations among all affected female rats after being treated with scheduled treatment for 7 and 14 days as well as control group are in Table 4. It can be seen that serum creatinine concentration was within the normal values in all groups before the infection. A substantial rise in serum creatinine levels (P≤0.05) was observed in all infected groups after 7 days of infection except the negative control group.

TABLE 4. Serum creatinine values of rats infected with *E. coli* O 157:H7 and treated with plantaricin and ciprofloxacin

Groups	Mean ±SE of Creatinine levels (mg/dl)		LSD value
	After 7 days of infection	After 14 days of infection	
Negative Control	0.650 ±0.08	0.650 ±0.08	0.055 NS
(A)	C a	B a	
Positive Control	1.317 ±0.11	1.148 ±0.12	0.194 NS
(B)	A a	A a	
Ciprofloxacin	1.067 ±0.09	0.737 ±0.07	0.206 *
(C)	AB a	B b	
Plantaricin	0.937 ±0.06	0.712 ±0.07	0.197 *
(D)	B a	B b	
LSD value	0.277 *	0.259 *	---

Means with different capital letters in the same column and small letters in the same row are significantly different. * (P≤0.05).

The impact of plantaricin on the kidneys affected by bacterial infection was assessed using a creatinine serum analysis. Additionally, there has been a surge in germ resistance to antibiotics; as a result, it is urgently necessary to consider as natural antibacterial compounds. Plantaricin has been demonstrated to be a spontaneous, secure antibacterial agent that is extremely efficient versus a variety of harmful

bacteria. It's have been employed as a replacement to other chemicals' antibacterial drugs [40,41] which noted that the initial defense against cationic bacteriocins is the anionic cell membranes of bacteria. Plantaricin is thus frequently employed to destroy specific bacteria by permeabilizing the cell membrane [42]. As compared to ciprofloxacin, plantaricin's ability to permeabilize membranes against *E. coli* O157 H7 was Noticed in this investigation [43]. plantaricin dissipated power, through electrolyte outflow and subsequent membrane permeation led to the suppression of intracellular ATP, which brought in cell death. The findings imply that plantaricin's constituents have some anti- *E. coli* action [44].

Treatment by plantaricin, which inhibits numerous cellular targets, has been proposed as a promising approach that may postpone the emergence of tolerance despite lowering dose and associated adverse reactions [45-46].Plantaricin has been shown to improve the bactericidal and inhibitory effects of conventional antibiotics at doses below the MIC which could decrease the danger of cytotoxic side effects and the emergence of antibiotic resistance. Using precise therapies in mixed forms is a beneficial and essential strategy that has the ability to increase the arsenal of available antibiotics versus infections and repurpose presently off-patent drugs that agree with [47]. Traditional antibiotics were significantly improved in clinical settings when synthetic peptides were present because they decreased the size of abscesses and improved bacterial clearance .Enhanced membrane permeability and improved antibiotic penetration are among the proposed underlying mechanisms [48]. The research being conducted makes the case for the ongoing development of plantaricin as possible treatments for the *E. coli* O157:H7 bacterium strain [49-50]

Conclusion

Extraction of plantaricin has nearly the same effect as antibacterial agent and safer when it was compared with ciprofloxacin , also its provides a powerful approach to optimize doses of antimicrobial drugs used against bacterial infectious diseases in clinical Veterinary Medicine.

Acknowledgements

Regarding the resources offered during sample processing, the authors are grateful to the heads of the physiology, biochemistry, and pharmacology departments at the college of veterinary medicine at the University of Baghdad.

Novelty Statement

The research's originality is the emphasis on the medical benefits of plantaricin, whose originates from *L. plantarm*, as well as gene sequences for treating UTIs brought on by *E. coli O157:H7* as a substitute of antibacterial drugs.

Authors Contribution

Everyone who wrote made an equal contribution. Conflicts of attraction: The authors have stated that they have none.

Abbreviations

E. coli O157:H7 = Escherichia coliO157H7

Vitek II System = automated Vitek 2 system

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دور البلانتراسين في علاج التهابات المسالك البولية في اناث الجرذان

علا حسون عبيد [1] وعلي حسين سليم [2]

[1,2] فرع الفسلجة والكيمياء الحياتية والادوية - كلية الطب البيطري - جامعة بغداد - بغداد - العراق .

[1] فرع الادوية - كلية الطب - جامعة الفلوجة - الانبار - العراق.

الغرض من هذا البحث هو دراسة تأثير البلانتاريسين على التهابات المسالك البولية المحدثة تجريبيا ببكتيريا *E.coli O157H7* في إناث الجرذان، والذي يتكون من خطوتين؛ تضمنت المرحلة الأولى عزل وتشخيص بكتريا *E.coli O157 H7* باستخدام الاختبارات البيوكيميائية ونظام VITEK II، بينما تضمنت الخطوة الثانية دراسة النشاط العلاجي لعقار البلانتاريسين (الذي تم عزله من بكتيريا *Lactobacillus plantarum* وتم تشخيصه وراثيا بواسطة (PCRضد عدوى المسالك البولية المحدثة تجريبيا. بواسطة *E.coli O157:H7* في 32 أنثى فأر (التي تم تقسيمها إلى أربع مجموعات متساوية)، ومقارنة هذه التأثيرات مع عقار سيبروفلوكساسين. أظهرت نتائج هذا البحث أن للبلانتريسين تأثير علاجي واضح في علاج التهابات المسالك البولية من خلال تأثيره على وزن الجسم وتحسين العلامات السريرية وكذلك عدد البكتيريا في البول ومستوى الكرياتينين في مصل إناث الجرذان مقارنة بالحيوانات، وكانت أكثر شديدة العدوى ببكتيريا *E.coli O 157;H7* التي أصيبت ببكتيريا *E.coli O157:H7* ولم يتم علاجها أو مع الحيوانات المعالجة بالسيبروفلوكساسين. هذا النشاط المضاد للبكتيريا الذي يتميز به البلانتاريسين بسبب تأثيراته المضادة للميكروبات الطبيعية والآمنة ضد مسببات الأمراض . *E.coli O157:H7*

الكلمات الدالة: الدور العلاجي للبلانتراسين ,القوارض أوالجرذان ، العوامل البكتيرية .