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Study of the Effectiveness of *Papaver* Sp. Alkaloids as Future Therapeutic Alternatives against *Enterococcus* Sp. Causing Hospital-Acquired Septicemic Infections

Lama Mohammed Ayoub Shbibe, Georgette Antranik Babojian

Department of Plant Biology, Faculty of Science, Damascus University, Damascus, Syria
Email: lama.mena1990@damascusuniversity.edu.sy, g.babojian@damasuniv.edu.sy

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Abstract

Background and Objective: In recent years, control of *Enterococcus* sp. It has been proven in the local medical environment to be a cause of acquired septicemia in various age groups, and medical instruments are considered an effective means of transmitting enterococcal septicemia, and catheters are at the forefront in terms of danger. Based on this risk, this study aimed to monitor the spread of *Enterococcus* sp., which causes blood poisoning acquired from catheters, and to compare its response to antibiotics with that of those isolated from clinical samples in children, as a first study locally. The effectiveness of alkaloids of different types of *Papaver* sp. In Syrian plants, they were tested against infection with this bacteria. **Materials and Methods:** The study dealt with two parts: The first part included collecting clinical samples from the University Children's Hospital in Damascus/bacterial diagnostic laboratories/then isolating and diagnosing the bacteria by following a set of tests to identify the most prevalent genera and species and comparing their prevalence rate with *Enterococcus*. The second part; It included collecting plant samples, confirming the species taxonomically, then extracting alkaloids from plant parts (fruit, stem, Flowers), then comparing the extent of resistance of bacterial strains to antibiotics compared to the *Enterococcus* sp., and then confirming the antibacterial activity of the *Papaver* sp. alkaloids against *Enterococcus* sp. **Result:** In its first part, the study confirmed the significant contribution of the *Enterococcus* sp. to infections acquired from various sources, largely in catheter tip infections (9.09%) and to a lesser extent in other sources (3.7%), The second part was to confirm the effectiveness of the alkaloid extract of the *Papaver* sp., especially the two species *Papaver syriacum* and *Papaver dubium*, against *Enterococcus* sp. with areole diame-

ters that ranged between (15 - 26 mm) for the fruit extract and at a minimum inhibitory concentration (3.12 - 6.25 mml) and then the stem (5 - 20 mm). And the effectiveness of the Flowers extract is very weak to almost non-existent. **Conclusions:** The catheter and medical sources surrounding the patient constitute a dangerous source of multi-resistant *Enterococcus* sp., which poses a real threat to the lives of children, with new mechanisms represented by colonization of the skin and the ability to form biofilms Surfaces of medical instruments, with are resistant to a wide range of antibiotics. As an alternative and effective modern source to limit its spread in the future, the alkaloid extract of the fruits and stems of the wild *Papaver* sp. has proven a strong antibiotic effect, especially the two types: *Papaver syriacum* and *Papaver dubium.*

Keywords

Catheters, Skin Ulcers, Acquired Infection, Multi-Resistant *Enterococcus* Sp., *Papaver* Sp. Alkaloids, Minimum Inhibitory and Lethal Concentration

1. Introduction

The safe mechanism for using catheters of all kinds has revolutionized the modern health system, especially the critical sectors. However, these catheters are closely linked to the factors that cause acquired bacterial and fungal septicemia, and today they occupy advanced ranks globally, among the medical environmental sources that threaten the lives of immunocompromised people, especially newborn children. Childbirth, and its risk increases with the increase in bacterial and fungal resistance to a wide spectrum of antibiotics and antifungals used in the treatment of infections acquired from the hospital environment, which prompted international research to shed light on the catheters used in health centers and work to make them more versatile and safe medical tools, and catheters in Medicine is; The process of inserting a metal or rubber tube into the human body to withdraw or inject fluids from and into body cavities, vessels, or various channels, or to insert surgical tools such as balloons, metal mesh, or various sensors, and they have different types: Urinary catheter: inserted into the urethra to empty the bladder. Ureteral catheterization, arterial catheterization, venous catheterization, cardiac catheterization, spinal cord catheterization, and dura catheterization are used in local anesthesia procedures. Thus, the cases of infection associated with it vary according to the type and intended application. It is also related to the skill of the individual who installs the catheter, the time period for its installation and replacement of the catheter, the physiological state of the patient, and the medical staff's adherence to the rules of protection and prevention while placing the catheter [1]. Thus, catheters have become one of the most important sources of globally acquired infections that threaten the lives of millions in health centers and may be associated with other systemic infections, most notably generalized sepsis. As the bacteria and fungi that cause these

infections gain multiple resistance to antibiotics, the volume of global research related to finding therapeutic alternatives has increased. New, especially the plant kingdom was in first place because of its great biodiversity. Therefore, international studies directed research into the chemical and pharmaceutical aspects of many plants with a medical history, with the aim of determining their applied properties in various medical fields (treatment - cosmetics - food), mentioning The properties that combat fungal and bacterial diseases have taken the lead in the global trend towards alternative medicine, especially in light of the continuous development of fungal and bacterial resistance to the group of manufactured and globally approved antibiotics, which has resulted in a wide spread of resistant bacterial and fungal species in various environmental that have become a threat to human life, in addition to Fear of unsafe and excessive use of antibiotics in many global societies.

Acquired sepsis: According to the Centers for Disease Control, it is defined as the presence of one type of bacteria or fungus active in the bloodstream and confirmed by a positive blood culture result. Septicemia infection is associated with high death rates around the world. Patients with acquired septicemia in the United States of America are estimated at approximately 250,000 cases annually. It is one of the top ten leading causes of death, and the mortality rate ranges from 12% in hospital cases to 80% in the intensive care unit [2]. Catheter-related sepsis (CRBSIs) Catheter-related bloodstream infections Catheter-related septicemia is among the most common types of hospital-acquired infections. Global statistics currently indicate that 15% - 30% of the total number of hospital-related septicemia cases are related to catheter infections. The observed increase in this Infection and the information accumulated around it are a complex medical aspect, which makes it necessary to analyze this information and statistics and search for new methods of prevention and protection to overcome the risk of hospital infections associated with catheters. The majority of CRBSIs are associated with central venous catheters (CVCs), and the relative risk of this infection with CVCs is 64% greater than with peripheral catheters [3]. Studies have confirmed that 60% of CRBSIs are caused by microorganisms already present on the patient's skin. This infection often arises in the emergency room and intensive care unit, where 5.3 infections occur in the bloodstream every thousand days of insertion of central venous catheters [4]. There are many factors that cause this infection, including the natural growth of the skin, and it may be the result of contamination of the tip of the catheters, the formation of bacterial biofilms, or Fungal infection of the internal surfaces of the catheters or through the fluids introduced into the catheters. If the result of the catheter implantation is positive but the result of the blood culture is negative, the infection is mainly due to the formation of biofilms inside the catheters. If the result of the catheter implantation results from (Staphylococcus aureus or Candida. sp.) In this case, monitoring and evaluation of cases of infective endocarditis is required [3]. Hemolytic and non-hemolytic Staphylococcus aureus strains, and *Enterococcus* sp. Gram-negative bacilli of all kinds and Candida sp. are the primary factors for

CRBSIs infection [5], and they remain until today, according to most international studies, and are Staphylococcus aureus, ranging from 10% to 36% [6]. Experimental treatment includes giving the patient antibiotic coverage for agents resistant to β-lactam antibiotics. The antibiotic coverage continues until the results of laboratory culture of the catheter tip or blood sample diagnosed with acquired septicemia appear, or taking swabs for the presence of skin ulcers that may result from the transmission of this infection and the antibiotic dose is adjusted. After confirming the results of laboratory culture, here the issue of CRBSIs infection faces two investigative problems, which are the multiple resistance of the pathogens to antibiotics, and the second; It is important to direct experimental treatment more precisely in order to protect patients, especially people with weakened immune systems, such as children or those residing in intensive care units in general [6], and based on the seriousness of this infection and its bad prognosis for global health.

2. Overview of *Papaver* Sp. Alkaloids

All global studies, ancient and modern, agree on the importance of the large and diverse alkaloid content of plants of the *Papaveraceas*. Despite the large number of these studies, they are still considered small compared to the great global spread of this family. The somniferous *Papaver* species, *P. somniferum*, ranked first in most international studies for a long period of time without shedding light on other *Papaver* species, especially since these studies emphasized only opiate alkaloids with narcotic effects due to their global importance on the economic side, and on the other hand, related to their dangerous effects. Illegal trade and agriculture have a burden on the international community.

However, microbiological research has recently been able to prove other beneficial aspects of the *P. somniferum* apart from its narcotic content, as it has proven its antibacterial effect as a new medicinal application aspect of this plant with a long medical history, according to a study conducted in Iran on the alkaloid extract of all parts. aerobic organisms, as they showed great effectiveness against a wide range of Gram-positive and Gram-negative bacteria. The study attributed the difference in effect between the different extracted alkaloids to the difference in the structure of the Gram-positive and Gram-negative bacterial cell walls [7]. Coming in second place is the *P. rhoeas*, in terms of the species spread globally and relied upon in many medical, industrial and commercial aspects, especially since the petal sleeve of this species has a very ancient medicinal and popular history and is still followed today in some societies without knowing the mechanisms. The truth about petal infusion in treatment; includes the treatment of tuberculosis, pneumonia, diphtheria, and urinary tract infections. In some Syrian regions, it is still used to treat chest infections and coughs in the winter. It is known colloquially in these areas as anemone without real taxonomic knowledge because it belongs to the *Papaver* sp. family and without separating it from other *Papaver* sp., and for this reason, international studies conducted

modern taxonomic studies at the genetic and chemical levels with the aim of determining the content of this type of non-narcotic alkaloids, and were able to prove its antibacterial ability to a group of germs, which explains its popular adoption to treat chest infections and various infections (urinary tract infections) and tuberculosis [8].

In parallel, the problem of antibiotics that are ineffective against most of the bacterial strains spread globally is ranked first in terms of the danger that threatens human life, and the noticeable increase in the spread and diversity of these bacterial strains, especially since some bacterial genera are still undiagnosed at the species level and are completely absent in statistical studies. In some countries of the world, its contribution to bacterial infections acquired from the surrounding environment that threatens the lives of millions annually has not yet been accurately monitored, which has often led to the use of broad-spectrum antibiotics for treatment. Global and local studies had to be directed toward finding safe natural sources. They will be effective pharmaceutical alternatives in the future. This study relied on the most important medicinal plants that are wildly widespread in the Syrian flora, as a future vector for *Enterococcus* spp., which has begun to record high incidence rates in most countries of the world in various health environments and has multiple resistance to antibiotics, starting from various oral infections all the way to various stubborn systemic infections, based on this, this first study locally aimed to determine the extent of the contribution of *Enterococcus* sp. In the pathogenesis of acquired septic infections resulting from the use of different catheters, comparing the results of bacterial isolation from catheter tips with clinical swabs taken from possible infectious sources in children, then testing the effectiveness of alkaloids from the group *Papaver* sp. against *Enterococcus* bacteria isolated from clinical samples compared to their antibiotic response to a group of antibiotics.

3. Materials and Methods

3.1. Bacterial Samples

The samples were collected from the University Children's Hospital during the period of time extending during the months (February-May) of the year 2023, in coordination with the hospital's bacterial diagnostic laboratory, and included samples (catheter tips—swabs from skin ulcers—cerebrospinal fluid) which were immediately cultured in a liquid medium. Nutritious. The name of the patient, the department, the date the sample was taken, and the source of the sample were recorded.

3.2. Isolation and Diagnosis Bacteria from Samples

Samples collected from catheter tips and swabs from skin ulcers were cultured in the prepared liquid medium in closed sterile tubes for 24 hours, observing the formation of turbidity, and then transferred onto Blood Agar (general nutrient-rich) medium (Tmmedia, India), and then relying on a set of selective media

(EMB, MaConky, Bil masculine) (Tmmedia, India).

3.3. Plant Samples

Were collected from the areas of (Deir Attiya - Damascus - Suwayda) in the period between 2019-2023, from February until April. The species were named according to local and international references [8]-[12]. The samples were dried in the dark for 5 weeks, and then the aerial parts were ground separately on both the fruit and the flower.

- Extraction of alkaloids: 2 grams of dried sample powder (stem - flower - fruit) were directly weighed and treated with 6 ml of chlorochloric acid and 30 ml of water, then boiled for 10 minutes. After that, the extract was filtered using filter papers with a diameter of 0.3 mm, and applied to the method with the three extracts (stem - fruit - flower).
- Detection of alkaloids in extracts: 2 ml of the filtered extract was transferred to a test tube (4 tubes) and then two drops of each of the four alkaloid reagents (Dragendorff, Hager, Hagner, and Mayer) were added.

3.4. Testing the Antibacterial and Antifungal Activity of the Extracts

Mueller-Hinton agar plates (Tmmedia, India) were prepared to first test bacterial susceptibility to a group of antibiotics using the Criby Power tablets method (Bioanalyse) (Cefotaxime, Ampicilln, Amoxicillin, Gentamicin, Meropenem, Imipenem, Amoxicillin/Clavulanic, Amikacin, chlorampnenicol, Doxyline, Penicillin G, Vancomycin, Cephalexin), and by following the wells method in a next step, the effectiveness of the three alkaloid extracts of six types of *papaver* sp. against *Enterococcus* sp. was studied, and then the minimum inhibitory and lethal concentration (MIC, MBC) of the most effective species against the same Bacteria was determined.

3.5. Statistical Section

An Excel worksheet was used to draw charts showing the distribution of samples and culture results, and calculate the percentage of *Enterococcus* sp. that appear in various clinical samples, compared to the rates of appearance of other gram-negative and gram-positive bacteria to determine the duration of their contribution to causing the infection, and also calculate the average diameters of the inhibition circles based on 3 replicates and calculate their standard deviation based on the T-test.

4. Results

4.1. Gram Negative Bacteria

Samples were collected from different departments at the Children's University Hospital, and they numbered 52 samples taken from catheter tips and swabs from skin ulcers, Table 1 and Table 2.

Table 1. Shows swabs and samples taken from different hospital departments.

Result	Gender	Data	Sample	NO
E. coli	male	3/1	Swab from infected wound	14
Pseudomonas aeruginosa	male	3/1	Swab from infected wound	15
Klebsiella pnumonia	female	2/1	Swab from infected wound	17
Staph. epdirmes	female	2/1	Swab from infected wound	18
E. coli	female	4/1	Swab from infected wound	19
***Enterococcus* sp.**	female	**2/1**	Swab from infected wound	**20**
Candida	male	7/1	Swab from infected wound	24
E. coli	male	7/1	Swab from infected wound	28
Klebsiella pnumonia	female	1/1	Swab from infected wound	29
Klebsiella pnumonia	female	10/1	Swab from infected wound	30
Klebsiella pnumonia	female	7/1	Swab from infected wound	32
Klebsiella pnumonia	female	7/1	Swab from infected wound	32
Klebsiella pnumonia	female	7/1	Swab from infected wound	34
Klebsiella pnumonia	male	22/1	Swab from infected wound	36
Klebsiella pnumonia + *Acintobacter bumanii*	male	22/1	Swab from infected wound	37
Klebsiella pnumonia + *Acintobacter bumanii*	male	22/1	Swab from infected wound	38
Klebsiella pnumonia + *Acintobacter bumanii*	female	21/1	Swab from infected wound	39
More than one type	female	23/1	Endocarditis	40
Klebsiella pnumonia	male	6/1	Lumbocele	27
More than one type	male	8/1	Lumbocele	22
More than one type	male	8/1	Swab from infected wound	23
More than one type	female	3/1	Lumbocele	16
E. coli	female	23/12	Encephalocele	11
Sterile	Male	5/1	CSF	26
Sterile	Male	8/1	CSF	31
Acintobacter bumanii	female	7/1	CSF	33
Acintobacter bumanii	female	7/1	CSF	35
Pseudomonas aeruginosa	Male	28/1	CSF	41
More than one type	Male	28/1	Swab from infected wound	42
Staphylococcus aureus	Male	24/1	Swab from infected wound	43
More than one type	female	28/1	Swab from infected wound	45

Continued

Enterococcus sp.	Male	**28/1**	**CSF**	46
E. coli	female	4/2	Swab from infected wound	47
E. coli	Male	3/2	Swab from infected wound	48
Klebsiella pnumonia	Male	3/2	Swab from infected wound	50
E. coli	Male	4/2	Swab from infected wound	51
Streptococcus sp.	Male	5/2	Swab from infected wound	52

Table 2. Shows samples of catheter tips taken from different hospital departments.

Result	Gender	Data	Sample	NO
Klebsiella pnumonia	female	6/7	Venous catheter	1
Staphylococcus aureus	female	23/7	Venous catheter	2
Sterile	female	22/7	Venous catheter	3
Staphylococcus aureus	male	23/7	Venous catheter	4
Sterile	female	25/7	Venous catheter	5
Pseudomonas aeruginosa	female	30/7	Venous catheter	6
Staph. epdirmes	female	30/7	Venous catheter	7
Staphylococcus aureus	female	30/7	Venous catheter	8
Enterococcus sp.	female	2/8	Urinary catheter	9
Streptococcus sp.	female	22/8	Venous catheter	10
Klebsiella pnumonia	female	22/8	Venous catheter	12
Streptococcus sp.	female	23/12	Cerebral catheter	13
Klebsiella pnumonia	female	2/1	Venous catheter	21
More than one type	male	29/1	Venous catheter	22
More than one type	male	29/1	Cerebral catheter	44
Candida sp.	male	5/2	Cerebral catheter	49

It demonstrates the diversity of possible sources of infection in the patient, which are added to or considered a cause of septicemia infection, which may cause septic infection associated with catheters of various types.

Table 1 that the samples numbered (17 - 30 - 32 - 34) in the first table and sample number 21 in the second table are samples belonging to the same patient, whose clinical condition was monitored during her stay in the hospital for treatment, and in coordination with the hospital laboratories, the catheter head was implanted and Then, successive samples were taken from skin ulcers in different areas of the body, and in line with the cultivation of a blood sample, and with identical positive culture results between the samples (blood - catheter tip - swabs from the thigh, forearm, and hand), it was noted that the *Klebsiella*

pneumonia type was dominant, and in complete agreement between the results of the hospital and the results of this study. Clinical symptoms of sepsis began to appear on January 2, with the patient's intravenous catheter being installed and positive blood culture results being given. Then, skin ulcers began to appear in various places on the body, including the catheter entry points. As previously mentioned, the culture results were completely identical between the samples, as is evident from This clinical case that the catheter tip was the primary cause of the spread of septic infection and the entry of the pathogen into the bloodstream through a bacterial species transmitted from the surrounding environment, which may be (the patient's skin - medical staff - hospital tools - beds).

The second case in this study showed that *Klebsiella pneumoniae* was the primary dominant infection, cross-fertilizing between catheter tips (33.3% - 27.27%) and different clinical samples, while it was noted that my species (*E. coli*, *Acintobacter bumanii*) appeared in clinical samples from swabs of skin ulcers. There were cerebrospinal fluid coelomates (29.63% - 7.41%), but they disappeared in the catheter tip samples. This is primarily due to the ability of these bacteria to participate in the formation of biofilms on the surfaces of medical instruments, while the bacteria isolated from the catheter tips included *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* Table 2.

4.2. Gram Positive Bacteria

And *Staphylococcus epidermidis* and *Streptococcus aureus*, are especially noticeable in the heads of urinary catheters and intersecting with clinical spaces. *Enterococcus* sp

In sample No. 20 showed a septic infection of a wound suppuration in parallel with clinical septic symptoms, giving a positive blood culture result and matching the culture result between the swab and the blood sample.

On the other hand, the study of this bacterium in the study showed that comparing the biological characteristics of the *Enterococcus* sp. isolated from clinical samples and the head of the urinary catheter differed only in terms of the type of hemolysis (one gave the beta type, which causes skin ulceration, and the second gave the gamma type isolated from the cerebrospinal fluid and the urinary catheter).

4.3. Fungi

The infection didn't just stop on bacterial species, it included fungal infections, especially the Candida sp. And only the tip of the catheters (9.09%), with a lower frequency than the bacterial genera and species so far, despite the great danger of Candida infection to the health sector, which has been indicated by international studies and research, especially the danger of the spread of multi-resistant fungal strains and the significant contribution of Candida to a wide spectrum of infections, including acquired infections. From the environment. Samples that yielded more than one bacterial genus were excluded from the sample results in case

of contamination occurring during taking the sample from the patient from the surrounding environment or from the patient's skin. (Figure 1 and Figure 2)

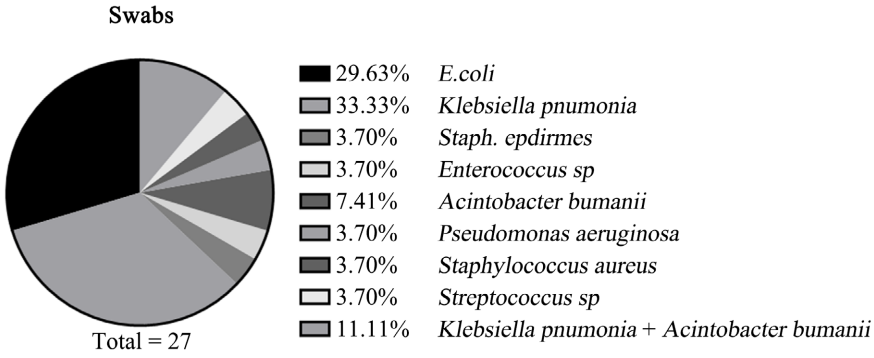

Figure 1. Shows the percentages bacteria isolated from clinical swabs.

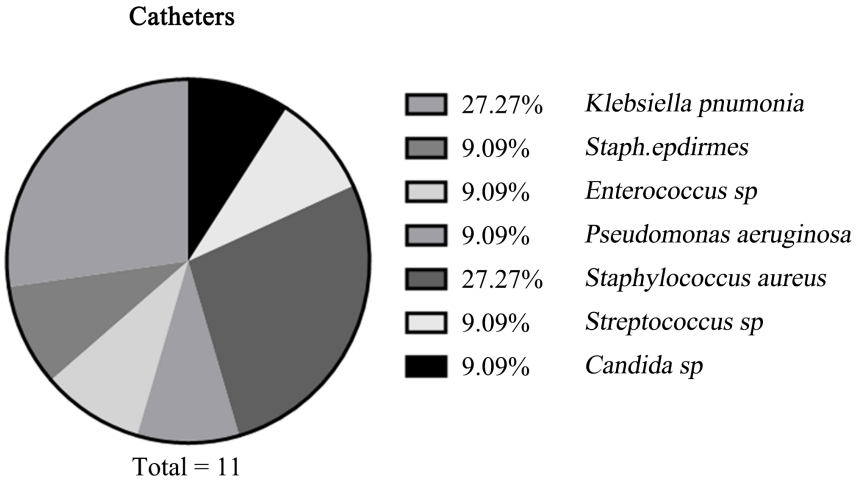

Figure 2. Shows the percentages of appearance of bacteria isolated from catheter tips.

5. Antibiotic Sensitivity Test

It is clear from the antibiotic susceptibility test that the bacteria showed complete resistance to most of the antibiotics commonly used in the treatment of septic infections and that the *Enterococcus* sp. occupied advanced ranks in terms of multiple and complete antibiotic resistance, with a difference between the hemolytic and non-haemolytic strains of the same bacterial genus, where the non-haemolytic strain was recorded. 100% complete resistance, while the current strain has shown sensitivity to some antibiotics. *Klebsiella pneumoniae* isolated from the blood, catheter tips, and body ulcers in the same patient showed identical results in the susceptibility test and was resistant to all antibiotics except Doxyline Table 3 and Table 4, which indicates that the source of the acquired infection is one. Following up on the patient's clinical condition, we find that the first septic symptoms appeared after the catheter was placed. Then, scattered ulcers appeared in the body, which were later accompanied by septicemia, as superficial infections that are limited to (the outlet of the peripheral or

central venous catheter or the location of the subcutaneous port of the catheter inside the blood vessels) are easily diagnosed by the presence of redness, swelling, pain, and sometimes purulent secretions. Such infections are treated effectively in the vast majority of cases by removing the catheter, and implanting the catheter tip or insertion site if pus is present and systemic symptoms of infection appear (e.g., fever, sepsis syndrome). The results of the susceptibility test for residual germs recorded a difference in response to antibiotics between the swabs and catheter samples (*Pseudomonas aeruginosa. Ecoli*), noting that the *Pseudomonas aeruginosa* isolated from the catheters was completely and multiple resistant to antibiotics, and the isolates from the swabs were sensitive to Imipenem and Amikacin Table 3 and Table 4, and this indicates Here, the sources of acquired infection are different, that is, the sources of contamination of catheters are different. On the other hand, there may be two different strains of *Pseudomonas* sp. spread in the same health center, and both of them contribute to causing the acquired infection from different sources. What is striking in the results of this study is the complete resistance to both *Enterobacter* sp. and *Acintobacter bumanii*, identically between catheter samples and clinical swabs in patients Table 3 and Table 4.

Table 3. Shows the results of the antibiotic susceptibility test for Gram-negative bacteria isolated from Swabes.

Aniboitic	Disk content (μg)	*Pseudomonas aeruginosa*		*E. coli*		*Enterobacter sp.*		*Klebsiella pneumonia*		*Acintobacter bumanii*	
		AV	*ST*	*AV*	*ST*	*AV*	*ST*	*AV*	*ST*	*AV*	*ST*
Cefotaxime	30 ug	0.1	0.11547005	0	0	0	0	0	0	0	0
Ampicilln	10 ug	0	0	0	0	0.35	0.4041452	0	0	0	0
Amoxicillin	25 mcg	0	0	0	0	0	0	0	0	0	0
Gentamicin	10 ug	0.05	0.05773503	0.2	0.2309401	0	0	0	0	0	0
Meropenem	10 ug	0	0	0	0	0	0	0	0	0	0
Imipenem	10 ug	9.9666667	0.05773503	0	0	0.3	0.5196152	0	0	0	0
Amoxicillin/ Clavulanic	20/10 mcg	0	0	0	0	0	0	0	0	0	0
Amikacin	30 mcg	4.8333333	0.28867513	18	0	0.1333333	0.2309401	0	0	0.1666667	0.2886751
chlorampnenicol	30 mcg	0.45	0.51961524	0.45	0.5196152	0.45	0.5196152	0.1	0.1154701	0	0
Doxyline	30 mcg	0	0	9.95	0.057735	0	0	10	0	0	0
Penicillin G	10 mcg	0	0	0	0	0	0	0	0	0	0
Vancomycin	30 mcg	0	0	0	0	0	0	0	0	0	0
Cephalexin	30 mcg	0	0	0	0	0	0	0	0	0	0

Table 4. Shows the results of the antibiotic susceptibility test for Gram-negative bacteria isolated from catheter tips.

Aniboitic	Disk content (μg)	*Pseudomonas aeruginosa*		*Enterobacter sp.*		*Klebsiella pneumonia*	
		AV	*ST*	*AV*	*ST*	*AV*	*ST*
Cefotaxime	30 ug	0	0	0	0	0	0
Ampicilln	10 ug	0	0	0	0	0	0
Amoxicillin	25 mcg	0	0	0	0	0	0
Gentamicin	10 ug	0	0	0	0	0	0
Meropenem	10 ug	0	0	0	0	0	0
Imipenem	10 ug	0	0	0	0	0	0
Amoxicillin/Clavulanic	20/10 mcg	0.3	0.5196152	0	0	0	0
Amikacin	30 mcg	0	0	0.1	0.1732051	0	0
chlorampnenicol	30 mcg	0.3	0.3464102	0	0	0.3	0.5196152
Doxyline	30 mcg	0	0	0	0	9.9	0.1154701
Penicillin G	10 mcg	0	0	0	0	0	0
Vancomycin	30 mcg	0	0	0	0	0	0
Cephalexin	30 mcg	0	0	0	0	0	0

This study showed, by examining the results of bacterial isolation from clinical swabs, catheter tips, and with blood samples from some patients, and by following up on the patient history, that catheters are a major cause of acquired septicemic infections in children and predispose to a general septicemic infection that threatens the child's life, especially since the bacteria isolated from these sources showed multiple and complete resistance. Regarding a wide range of antibiotics used to treat acquired septic infections, gram-positive bacteria have recently begun to occupy first ranks in terms of prevalence and antibiotic resistance Table 5 and Table 6, and to this day, oral diagnosis of septic infections is limited to specific bacterial genera without shedding light on other bacterial genera, which are universally considered important factors in causing infection. Bacterial bacteria are diagnosed locally (gram-negative bacteria) without precise determination of the genus or type to accurately guide subsequent antibiotic treatment. The problem of undirected antibiotic coverage is a local and global problem in the treatment of acquired septic infections, which relies first on experimental antibiotic coverage in treatment until the diagnosis results appear. The laboratory and the patient's antibiotic coverage are changed again, thus exposing the child to an experimental dose of antibiotics, which means contributing significantly to the germs becoming resistant to the future and thus a large spread in medical environments of multi-resistant bacteria.

Table 5. Shows the results of the antibiotic susceptibility test for Gram-positive bacteria isolated from samples.

Aniboitic	Disk content (μg)	*Staphy. aureus* Non-hymolysis		*Staphy. aureus* hymolysis		*Staphy. epdirmes* Clinical-sample		*Streptococcus sp.* Clinical-sample		*Staphy. epdirmes* catheter		*Streptococcus sp.* catheter	
		AV	ST	AV	ST	AV	ST	AV	ST	AV	ST	AV	ST
Cefotaxime	30 ug	14.9	0.1154701	0.45	0.5196152	0	0	0	0	0	0	0	0
Ampicilln	10 ug	0	0	0	0	0	0	0	0	0	0	0	0
Amoxicillin	25 mcg	10	0	0	0	0	0	10	5.7735027	0.25	0.2886751	0	0
Gentamicin	10 ug	0	0	0	0	0	0	4.75	0.2886751	0	0	0	0
Meropenem	10 ug	0	0	0	0	0	0	0	0	0	0	0	0
Imipenem	10 ug	0	0	0	0	0	0	0	0	0	0	0	0
Amoxicillin/Clavulanic	20/10 mcg	19.966667	0.057735	0.2	0.3464102	0.1	0.1732051	0	0	0.3	0.5196152	0.3666667	0.6350853
Amikacin	30 mcg	0	0	0	0	0	0	0	0	0	0	0	0
chlorampnenicol	30 mcg	18	0	0	0	0	0	0	0	0	0	0	0
Doxyline	30 mcg	20.1	0.1154701	0	0	0.4	0.4618802	21.85	0.1732051	0	0	22.2	0.2309401
Penicillin G	10 mcg	0	0	0	0	0	0	0	0	0	0	0	0
Vancomycin	30 mcg	0	0	0	0	0	0	10.75	0.2886751	0	0	4.9	0.1154701
Cephalexin	30 mcg	15	0	0	0	0.65	0.7505553	0	0	0	0	0	0

Table 6. Shows the results of the antibiotic susceptibility test for *Enterococcus* sp. isolated from Samples.

Aniboitic	Disk content (μg)	*Enterococcus sp.* Non-hymolysis CSF		*Enterococcus sp.* Non–hymolysis Catheter		*Enterococcus sp.* Hymolysis Swab from infected wound	
Cefotaxime	30 ug	AV	ST	AV	ST	AV	ST
Ampicilln	10 ug	0	0	0	0	0	0
Amoxicillin	25 mcg	0	0	0	0	10	0
Gentamicin	10 ug	0	0	0	0	0	0
Meropenem	10 ug	0	0	0	0	0	0
Imipenem	10 ug	0	0	0	0	9.75	0
Amoxicillin/Clavulanic	20/10 mcg	0	0	0	0	0	0
Amikacin	30 mcg	0	0	0.2333333	0.4041452	7.2	0.3464102
chlorampnenicol	30 mcg	0	0	0	0	0	0
Doxyline	30 mcg	0	0	0.2	0.2309401	10	0
Penicillin G	10 mcg	0.45	0.5196152	0	0	19.75	0.2886751
Vancomycin	30 mcg	0	0	0	0	0	0
Cephalexin	30 mcg	0.25	0.2886751	0	0	0	0

6. Results of Testing the Antimicrobial Effect of Alkaloid Extracts

Results of testing the effectiveness of alkaloid extracts: Six species of wild *Papaver* sp. were identified in the collection areas (Damascus - Deir Attiya - As-Suwayda) and named according to international references and florists [9]-[15]. It was found that they belong to the following species (*Papaver hybridum*, *Papaver rhoeas*, *Papaver dubium*, *Papaver polytrichum*, *Papaver umbonatum*, *Papaver syriacum*), the powder of the fruit, stem and flower of each of the previous species was relied upon, and the presence of alkaloids was confirmed by adopting four types of specific reagents for alkaloids, and all of them were positive in the extracts of the fruit and petals, with different degrees of positivity **Table 7**.

Table 7. Shows the results of detecting the presence of alkaloids in the three extracts using four types of alkaloid reagents.

Species / Fruit	*Papaver syriacum*	*Papaver umbonatum*	*Papaver polytrichum*	*Papaver dubium*	*Papaver rhoeas*	*Papaver hybridum*
Dragendrov	+++	++	+	+++	++	+
Mayer	+++	++	+	+++	++	+
Hagner	+++	++	+	+++	++	+
Hager	+++	++	+	+++	++	+
Species / Flowers	*Papaver syriacum*	*Papaver umbonatum*	*Papaver polytrichum*	*Papaver dubium*	*Papaver rhoeas*	*Papaver hybridum*
Dragendrov	+++	++	+	+++	+	+

Continued

Mayer	+++	++	+	+++	+	+
Hagner	+++	++	+	+++	+	+
Hager	+++	++	+	+++	+	+
Species / Stem	*Papaver syriacum*	*Papaver umbonatum*	*Papaver polytrichum*	*Papaver dubium*	*Papaver rhoeas*	*Papaver hybridum*
Dragendrov	+++	++	+	+++	++	-
Mayer	+++	++	+	+++	++	-
Hagner	+++	++	+	+++	++	-
Hager	+++	++	+	+++	++	-

A study of the effectiveness of the alkaloid extract of powdered plant parts of six species (*Papaver hybridum*, *Papaver rhoeas*, *Papaver dubium*, *Papaver polytrichum*, *Papaver umbonatum*, *Papaver syriacum*), shows that the alkaloid fruit extract of all the previously mentioned *Papaver* species studied is the most effective as an antibacteral for *Enterococcus* sp., which causes various acquired infections (skin and urinary infections), with great activity against the hemolytic strain (type β), with areola diameters that ranged between (15 - 26 mm) at 100% concentration and (10 - 20 mm) at 50% concentration, and in correlation with the results of the antibiotic sensitivity test. A response to antibiotics (Cefotaxime, Ampicilln, Meropenem, Amoxicillin/Clavulanic, chlorampnenicol, Doxyline,) was recorded, while the same extract had less activity against the non-haemolytic strain (Type γ) and the diameters of areolas ranged between (9 - 20 mm) at the concentration of 100% and (5 - 10 mM) at a concentration of 50% and with complete antibiotic resistance to all antibiotics applied. Coming in second place in terms of effectiveness is the stem alkaloid extract, with less antifungal activity, but still higher against hemolytic *Enterococcus* sp. than the other strain. It appears from projecting the results of alkaloid detection with the effectiveness test on the flower extract that its alkaloid content was high in all species, especially The two species (*Papaver dubium*, *Papaver syriacum*), but in contrast, it was the least effective as an antibacterial for *Enterococcus* sp. infection, with no effectiveness in some speciess (*Papaver hybridum*, *Papaver polytrichum*) Table 8.

Table 8. Shows the results of testing the effectiveness of the three extracts against the two strains of *Enterococcus* hemolytic and non-haemolytic (*Enterococcus* 1: beta-hemolytic type, *Enterococcus* 2: non-haemolytic).

Fruit / Species		*Papaver syriacum*	*Papaver umbonatum*	*Papaver polytrichum*	*Papaver dubium*	*Papaver rhoeas*	*Papaver hybridum*
Enterococcus 1	100%	25 ml	15 ml	22 ml	26 ml	20 ml	15 ml
	50%	19 ml	10 ml	18 ml	22 ml	15 ml	10 ml
Enterococcus 2	100%	20 ml	9 ml	10 ml	15 ml	12 ml	10 ml
	50%	10 ml	2 ml	0 ml	5 ml	8 ml	5 ml

Continued

Species / Flowers		*Papaver syriacum*	*Papaver umbonatum*	*Papaver polytrichum*	*Papaver dubium*	*Papaver rhoeas*	*Papaver hybridum*
Enterococcus 1	**100%**	12 ml	10 ml	0 ml	20 ml	8 ml	0 ml
	50%	5 ml	0 ml	0 ml	10 ml	5 ml	0 ml
Enterococcus 2	**100%**	10 ml	0 ml	0 ml	10 ml	5 ml	0 ml
	50%	5 ml	0 ml	0 ml	5 ml	0 ml	0 ml
Species / Stem		*Papaver syriacum*	*Papaver umbonatum*	*Papaver polytrichum*	*Papaver dubium*	*Papaver rhoeas*	*Papaver hybridum*
Enterococcus 1	**100%**	20 ml	10 ml	10 ml	20 ml	10 ml	/
	50%	10 ml	5 ml	5 ml	15 ml	0 ml	/
Enterococcus 2	**100%**	15 ml	7 ml	0 ml	10 ml	10 ml	/
	50%	8 ml	0 ml	0 ml	5 ml	0 ml	/

The summary of the results of this study confirmed that the two wild species (*Papaver dubium*, *Papaver syriacum*) of the *Papaver* sp. are widespread in the Syrian flora; They have the highest alkaloid content and are the most effective as antibacterial agents against the various *Enterococcus* sp. species that cause septic infections in children, with similar areola diameters on solid media. Therefore, the study of the antibacterial effect of these two species was completed by determining the minimum inhibitory and lethal concentration (MIC, MBC) of the three extracts Table 9, and it was found that the *Papaver* species Dubium is the most effective, especially the fruit extract, against both strains, then the stem extract, with very little effectiveness, and parallel to the results of direct effectiveness on solid media comes flowersl extract, equally between the two species (*Papaver dubium*, *Papaver syriacum*).

Table 9. Shows the results of the test to determine the minimum inhibitory and lethal concentration of extracts of the two species *Papaver syriacum and Papaver dubium* against the beta-hemolytic *Enterococcus* strain. (*Enterococcus* 1: beta-haemolytic, *Enterococcus* 2: non-haemolytic).

Species / Fruit	*Papaver syriacum*	*Papaver dubium*	Species / Fruit	*Papaver syriacum*	*Papaver dubium*
MIC	*Enterococcus* 1	6.25 mul	MIC	*Enterococcus* 2	12.5 mul	3.12 mul
MBC		12.5 mul	MBC		25 mul	6.25 mul
Species / Flowers	*Papaver syriacum*	*Papaver dubium*	Species / Flowers	*Papaver syriacum*	*Papaver dubium*
MIC	*Enterococcus* 1	25 mul	MIC	*Enterococcus* 2	25 mul	25 mul
MBC		50 mul	MBC		50 mul	50 mul
Species / Stem	*Papaver syriacum*	*Papaver dubium*	Species / Stem	*Papaver syriacum*	*Papaver dubium*
MIC	*Enterococcus* 2	12.6 mul	MIC	*Enterococcus* 2	25 mul	12.6 mul
MBC		25 mul	MBC		50 mul	25 mul

7. Discussion

This initial study stopped when a group of septic cases resulting from catheter tip infections were compared with samples from different clinical swabs as sources of septic infection. The results of this study are divided at the medical microbiological level by investigating the sources of infection in septic catheters into three important results that intersect with many international studies.

First, it is evident from the correspondence of the results of implantation of the catheters with clinical sensors with blood samples in some patients and the follow-up of the septic medical history and the results of the susceptibility test. Catheters are an important and dangerous source of many gram-negative and gram-positive bacteria and fungi as well.

Secondly; the difference in the appearance of bacterial species between the tips of catheters and other clinical samples is due to the extent of the ability of these species to form biofilms on the surfaces of medical equipment. Therefore, we find that there is an absence of *E. coli* and *Acintobacter bumanii* in the catheter samples and a high frequency in other clinical samples.

Third; Susceptibility testing of some bacterial species isolated from different sources confirmed that some of the bacteria contributing to the formation of biofilms inside catheters were completely resistant compared to their counterparts, which were completely similar in biological characteristics, but showed sensitivity to a group of antibiotics when isolated from other clinical sources, and this is confirmed locally.

The results of a number of international studies on the importance of accurately identifying the sources of germs acquiring complete antibiotic resistance. Are they acquired from the environment as a result of exposure to a wide spectrum of chemicals? Or is it acquired from the undirected application of antibiotics, especially broad-spectrum antibiotics, during experimental antibiotic coverage? It appears from some of the results of this study and according to similar international studies that germs carried on the skin of children, workers, or surfaces adjacent to them acquire complete resistance after colonizing the surfaces of critical medical instruments. Or semi-critical and begins to form biofilms on them that are more resistant to surrounding factors and their transmission to the bloodstream, urinary tracts and brain (meninges), and exposure to doses of experimental broad-spectrum antibiotics acquires this complete resistance [16], as a study conducted in the United States of America confirmed that the borne *Staphylococcus epidermidis* On the patient's skin, they have become one of the important pathogens in hospitals, and about 80% of these strains, which are part of the normal flora after being isolated from septic clinical samples, showed resistance to methicillin and, more recently, resistance to vancomycin [17], and vancomycin-resistant *Staphylococcus aureus* has also recently been reported. And isolated from intravenous catheters, these results of international studies intersect with this study with regard to *S. aureus* and *Enterococcu* sp., especially those isolated from urinary and venous catheters. Studies have shown that *En-*

*terococcu*s sp. in general has acquired resistance to most aminoglycosides. The increasing prevalence of *Enterococcus* sp. that cause urinary catheter infections and are resistant to vancomycin is a source of great concern that requires the application of other antibiotics such as tetracycline, rifampin, chloramphenicol, or quinupristin-dalfopristin, depending on the susceptibility of the isolated bacteria [18].

According to the results of this study, *Enterococcus* sp. are still susceptible to chloramphenicol only. Hemolytic strain While the strain in the case, isolated from a clinical sample and a urinary catheter, was 100% resistant despite its relatively low virulence, *Enterococcus* sp. have recently emerged as major pathogens in hospitals and are currently the fourth leading cause of hospital-acquired infections, including Including those associated with intravascular catheterization. Repeated use of these medical devices is often associated with serious complications, including catheter-related bloodstream infections (CRBSIs), and their ability to form biofilms on the surfaces of catheters. Furthermore, in addition to the high level of resistance to penicillin, ampicillin, and aminoglycosides, a significant increase in enterococcal resistance to vancomycin has recently been observed in most clinical settings. Clinical strains that exhibit new mechanisms of acquired antibiotic resistance are frequently isolated. *Enterococcus* sp. has a great ability to Transfer these resistance traits to other species and even to other bacterial genera. The importance of the second part of this study stems from the seriousness of previous results of enterococcal resistance, which is the search for future sources of antibodies that are more diverse and safer in treating the resulting infections or in combating biofilms formed on the surfaces of medical tools. The results of this study also showed that the extract of *Papaver* sp. It has alkaloids that are effective against these bacteria, especially the two types (*Papaver dubium and Papaver syriacum*), which are of great importance in the future, as this study is considered the first locally in the microbiological application of extracts of the wild *Papaver* sp. In contrast, international studies have mostly proven the effectiveness of extracts of the two species, *Papaver somniferum* and *Papaver rhoeas*, as effective antibacterial agents against a wide range of Gram-positive and Gram-negative bacteria [19] [20]. Returning to international studies also in the same field, we find that many studies have confirmed the effectiveness of antifungal extracts. *Papaver*e S. Alkaloids against a wide range of multi-resistant Gram-negative and Gram-positive bacteria [21].

Previous results support the importance of the *Papver* sp. and its various wild species locally on the economic and medical levels, especially with its traditional use. Therefore, the study of its physiological or medicinal activities must be expanded, and this is what prompted international scientists and researchers to extract and purify all the known effective components from the various plant organs and then study The properties of the substance and its chemical characteristics, determining the plant composition, and conducting research to study the toxicological and therapeutic effects, the permissible doses, and the reasons for its use or not.

8. Conclusions

1) Catheters are a dangerous source of septic infections acquired from sanitary environments, and bacteria that form biofilms acquire complete resistance to the antibiotics used in oral coverage.

2) The study confirmed the ability of *Enterococcus* sp. to colonize the surfaces of medical instruments and form multi-resistant antibiotic-resistant biofilms.

3) The study was able to confirm the presence of six species of wild *Papaver* sp. widespread in the Syrian flora with a high alkaloid content in all plant parts.

4) The study demonstrated that the alkaloid extract of the fruits and stem of the two *Papaver* sp. species, *Papaver dubium and Papaver syriacum*, has great effectiveness against various multi-resistant *Enterococcus* strains isolated from various health sources.

9. Recommendations

1) Expanding local statistical studies to monitor the sources of the spread of multi-resistant bacteria and fungi and the extent of their contribution to causing acquired infections in all their forms.

2) Using molecular methods to accurately identify the types of *Enterococcus* sp. causing septicemic infections acquired in Syrian hospitals.

3) Conduct an extensive taxonomic study of the species of *Papaver* sp. widespread in the Syrian flora and examine in detail their medicinal benefits, especially their antibacterial and antifungal activity.

4) Future studies are directed at the possibility of applying other alkaloid extracts from *Papaver* sp. that may be more effective as antifungal agents.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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