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Synergistic effect of aqueous and alcoholic extracts of *L. nobilis*, *R. officinalis* and *Q. rubra* plants against bacteria isolated from burn patients

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Abstract
This study was performed at the Faculty of Science / University of Kufa from November 2022 to March 2023 designed to investigate the ability of Synergistic effect of aqueous and alcoholic extracts of L. nobilis, R. officinalis and Q. rubra plants against bacteria isolated from burn patients and hhe chemical composition of each plant is known. Three concentrations of methanol, hexane, cold water and hot water extracts (100, 200 and 400) mg/ml were performed.
Sixty-eight samples were collected from the Burns Medical Center in Najaf Governorate. Males and females in different age groups. 35 isolates of Pseudomonas aeruginosa, 18 isolates of Staphylococcus aureus and 15 isolates of Klebsiella pneumonia were tested. Ten antibiotics were selected in the antibiotic sensitivity test. The results showed that all three concentrations had good antibacterial effect. Also, the hot water solvent was found to be more effective on Sido bacteria with a rate of 37.167 ± 0.22mm. The results also showed that P. aeruginosa, and n-hexane solvent gave the highest rate of inhibition diameter against S. aureus bacteria 37.333 ± 0.36 mm while for K. pneumonia bacteria methane solvent was the highest 33.500 ± 0.14mm. The study highlights the synergistic effect of combining plant extracts, which outperforms individual plant extracts and even some antibiotics, such as Imipenem. The results emphasize the potential of these plants as alternatives to conventional antibiotics, particularly in combating antibiotic-resistant bacteria. Overall, these findings support the potential use of L. nobilis, R. officinalis, and Q. rubra as effective antimicrobial agents in the treatment of resistant bacterial infections.

Keywords: Antimycotic activity, minimum inhibitory concentration, *Argemone mexicana* L.

Introduction
Medicinal plants are less toxic and less harmful than industrial materials. Given their special importance for the safety of societies, many research centers are interested in plant therapy. Healing with medicinal plants is mainly due to the existence of various and complex chemicals formed in the plant as secondary metabolites, and they are classified as glycosides, alkaloids, flavonoids, saponins, carbohydrates and essential oils (Mai *et al.*, 2020) [28]. The spread of multidrug-resistant strains of bacteria and the less number of drugs available makes it necessary to discover new classes of antibacterial and also because antibiotics attack pathogenic bacteria as well as natural bacteria, such as those present in the intestine, respiratory system and skin, there is a need for new antibiotic discovery safe. Chemical components of the plant medicinal are the most important for pharmaceutical companies. People are interested in medicines prepared from plants due to their little or no side effects, cheap and almost available compared with synthetic drugs. It has been proven that many medicinal plants in Iraq contain compounds that have antimicrobial activity that can be an alternative to antibiotics. Akcan *et al.* in (2017) [2] pointed out that the dried *L.nobilis* leaves are widely used in meat and spice products as well as food preservatives as a result of their effectiveness against germs, also leaves has antimicrobial activity and antibacterial Gram negative and Gram positive (Cherrat *et al.*, 2014) [11]. Essential oil has a treatment for diabetes and an effective antioxidant activity, which can be attributed to the presence of phenol compounds (Vijayakumar *et al.*, 2016) [39]. *R. officinalis* it is a common household plant grown in many parts of the world. It is used for food flavor, beverage drink, as well as in cosmetics (Wollinger *et al.*, 2016) [40]. The antimicrobial activities of *R. officinalis* were good against dermatophytic and pathogenic bacterial (Jahani *et al.*, 2016) [21].

The leaf extract antibacterial activity for oral pathogen (Bernardes *et al.*, 2010) [9]. Most of the pharmacological effects of *R. officinalis* are due to the main chemical components, which include carnisole, carnosic acid, ursolic acid, rosmarnic acid, and caffeine acid these compounds have antioxidant effect and plays a major role in many chronic diseases such as cancer and coronary heart disease (Halliwell and Gutteridge, 2015) [14]. Its pharmacological effects of *Q. rubra* were evaluated and found to have had antibacterial, anti-inflammatory, anti-diabetic and antioxidant (Skrypnik *et al.*, 2019) [36]. Among its medical uses are wound healing, anti-MRSA, antifungal, antiparasitic and anti-digestive effects (Sati *et al.*, 2017) [35], and also to treat various diseases such as bleeding, shortness of breath, dysentery and asthma (Desprez *et al.*, 2014) [12]. *Q. rubra* has shown a broad-spectrum factor, which can be used against Gram positive and Gram-negative bacteria and fungi (Hamad *et al.*, 2017) [15].

Methods

Plant Collection and Preparation: The parts of used dried plants were purchased from local markets in the city of Najaf. After that it was cleaned and isolated from foreign materials, crushed by an electrical grinder and then the powder was collected in nylon bags and kept in the laboratory at room temperature until use**.**Then the three powders were mixed in equal proportion (1: 1: 1) in order to obtain a mixture result for the plants used. Preparation of Plant Extracts: (Harborne, 1984). Concentration of Plant Extracts (Al-Janabi and Semysim, 2020) [16]. Preliminary phytochemical for the extracts: (Mulla and Swamy, 2010) [29]. Specimens Collection: (Al-janabi and Aljanaby, 2024b) [3, 4] Effectiveness Test of Plants Extracts: (Aljanaby, 2013) [7].

Statistical Analysis: Statistical analysis was made using (graph pad prism version 10) computer software according to T- test, the mean value and standard error (SE) for each value was determined. *P.* value less than the 0.05 level of significance considered statistically significant (Al-janabi and Aljanaby, 2024a) [3].

Results

Table 1: Represents phytochemical components present in casings fruit of Q. rubra, the leaves of *L. nobilis* and leaves R. officinalis using the following solvents (cold water, hot water, methanol and n-hexane).

Detection of compound	casings fruit of Q. *rubra*.				leaves *R. officinalis*				leaves *L.nobilis*.			
	C.w	H.w	Me.	He.	C.w	H.w	Me.	He.	C.w	H.w	Me.	He.
Alkaloids	+	-	-	-	-	-	-	-	+	+	-	-
	+	+	+	+	+	+	+	+	+	+	+	+
Phenols	+	+	+	+	+	+	+	+	+	+	+	-
Flavonoids	+	+	+	+	+	+	+	-	+	+	+	-
Glycosides	+	+	+	-	+	+	+	-	+	+	-	-
Tannins	+	+	+	+	+	+	+	+	+	+	+	-
Terpenes	+	+	+	+	+	+	+	+	+	+	+	+
Saponins	+	+	-	-	+	+	-	-	+	+	-	-

(+): Present, (-): Absents, (C.W): cold water, (H.W): hot water, (ME): methanol, (HE): n-hexan

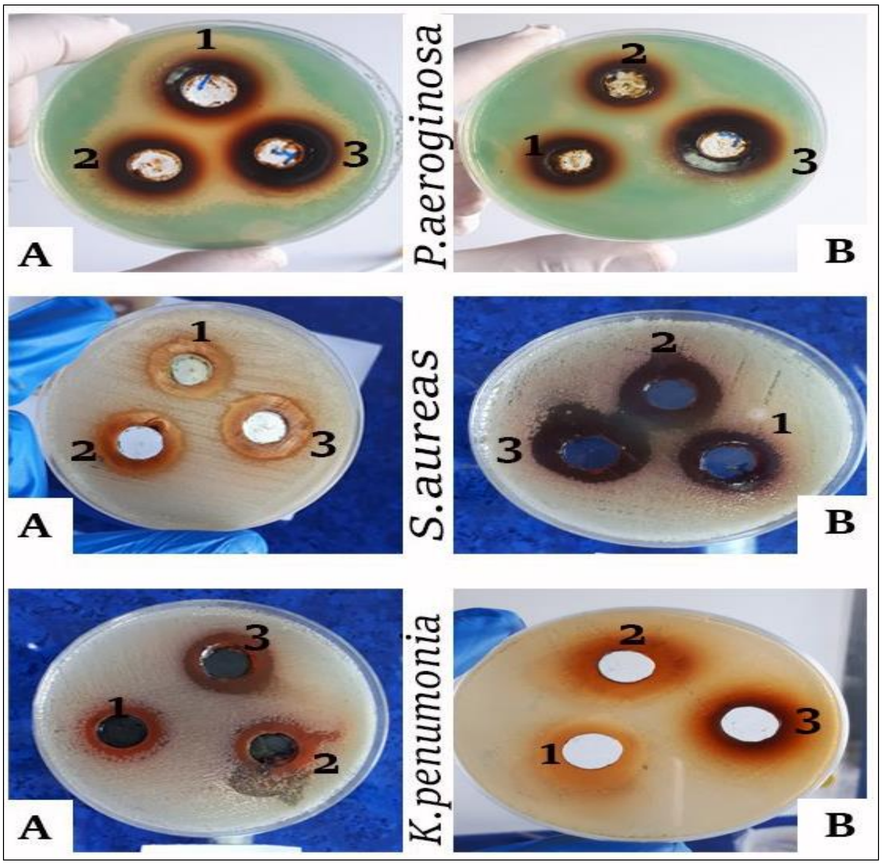

Fig 1: Effect of Mixture extracts on pathogenic bacteria isolated from patients with burn infections (1): 100 mg/ml (2): 200 mg/ml (3): 400 mg/ml (A): n-Hexan (B): Methanol extract

Table 2: Resistance pattern of most dominant pathogenic bacteria isolated from patients with burn infections.

No.	Antimicrobials	*P.aeruginosa* (35 isolates)	*S.aureus* (18 isolates)	*K.pneumonia* (15 isolates)
1	Amikacin 30 mg	13 (37.1)	7 (38.8)	5 (33.3)
2	Augmantin 30 mg	35 (100)	18 (100)	15 (100)
3	Ceftriaxon 30 mg	30 (85.7)	15(83.3)	10 (66.6)
4	Chloramphenicol 30 mg	35 (100)	17 (94.4)	14 (93.3)
5	Erythromycin 10 mg	18 (51.4)	9 (50)	11 (73.3)
6	Imipenem 10 mg	3 (8.5)	1 (5.5)	1 (6.6)
7	Nitrofurantein 300 mg	28 (80)	15 (83.3)	13 (86.6)
8	Norfloxacin 10 mg	20 (57.1)	9 (50)	9 (60)
9	Rifampin 5 mg	35 (100)	10 (55.5)	15 (100)
10	Trimethoprim 5 mg	35 (100)	18 (100)	15 (100)

Data presented as numbers and percentage of pathogenic bacterial isolates that were resistant to antimicrobials: no. (%).

Table 3: Evaluation of antibacterial activity of Mixture three plants effects of against pathogenic bacteria isolated from patients with burn infection.

Mixture of three plants extracts					
Pathogenic bacteria	**Concentration**			**P value**	
	100 mg/ml	**200 mg/ml**	**400 mg/ml**		
	Cold water extracts, M±SE mm			**A**	**B**
P.aeruginosa	21.750 ± 0.144	24.333 ± 0.363	30.500 ± 0.288	0.0027**	0.0002***
S.aureus	23.000 ± 0.288	26.750 ± 0.288	27.250 ± 0.144	0.0008***	0.1963
K.pneumonia	24.317 ± 0.092	30.283 ± 0.116	31.500 ± 0.144	< 0.0001***	0.0028**
Hot water extracts, M±SE mm				A	B
P.aeruginosa	27.500 ± 0.433	29.667 ± 0.300	37.167 ± 0.220	0.0147*	< 0.0001***
S.aureus	25.533 ± 0.260	27.000 ± 0.057	30.833 ± 0.363	0.0053**	0.0005***
K.pneumonia	25.733 ± 0.274	29.567 ± 0.290	32.500 ± 0.144	0.0007***	0.0008***
Methanol extracts, M±SE mm				A	B
P.aeruginosa	21.750 ± 0.288	24.250 ± 0.288	30.500 ± 0.144	0.0036**	< 0.0001***
S.aureus	27.583 ± 0.363	32.500 ± 0.144	33.250 ± 0.144	0.0002***	0.0213*
K.pneumonia	24.733 ± 0.303	28.167 ± 0.220	33.500 ± 0.144	0.0008***	< 0.0001***
n-Hexane extracts, M±SE mm				A	B
P.aeruginosa	24.500 ± 0.288	29.833 ± 0.166	32.333 ± 0.333	< 0.0001***	0.0026**
S.aureus	28.583 ± 0.220	32.500 ± 0.288	37.333 ± 0.363	0.0004***	0.0005***
K.pneumonia	21.583 ± 0.220	27.000 ± 0.288	29.667 ± 0.440	< 0.0001***	0.0072**

M±SE:Mean± standard error of diameters of inhibition zone in millimeters, A: Compare between concentration 100 and 200, B: Compare between concentration 200 and 400, *: significant difference at *P* value less than 0.05%.

Table 4: Comparison in diameters of inhibition zone in mm between imipenem 10mg and all plants extracts in (400 mg/ml) against three pathogenic bacteria isolated from patients with burns infections. R=3.

Pathogenic	Diameters of inhibition zone (mm) ± standard error						*P* value			
Bacteria	Type of plant	Cold water	Hot water	Methanol	n-Hexane	Imipenem 10mg	A	B	C	D
P.aeruginosa	mixture	30.500 ± 0.28	37.167 ± 0.22	30.500 ± 0.14	32.333 ± 0.33	33.292 ± ***0***.17	0.0015*	0.0006**	0.0088*	0.685
S.aureus	mixture	27.250 ± 0.14	30.833 ± 0.36	33.250 ± 0.14	37.333 ± 0.36	25.357 ± 0.07	0.0003***	0.0001***	< 0.0001***	< 0.0001***
K.pneumonia,	Mixture	31.500 ± 0.14	32.500 ± 0.14	33.500 ± 0.14	29.667 ± 0.44	29.333 ± 0.66	0.0337*	0.0097**	0.0036**	0.6981

A: Compare between Cold water and Imipenem 10mg, **B:** Compare between Hot water and Imipenem 10mg, **C:** Compare between Methanol and Imipenem 10mg, **D:** Compare between n-Hexane and Imipenem 10mg, *: significant difference at value less than 0.05

Discussion

That plants *L. nobilis, R. officinalis,* and *Q.rubra* are all rich in alkaloids, phenols, terpenes and tannins. The presence of these phytochemical compounds indicates that these plants have different medicinal properties in addition to being used as good antimicrobial (Al-Snai, 2019) [6]. The characteristic of resistance to bacterial isolates for burn patients is one of the most important and major medical problems, especially if they are resistant to more than one antibiotic and thus find it difficult to choose the appropriate treatment (Laxminarayan *et al.*, 2013) [26]. Medicinal plants are nowadays considered as the important source of materials used in preparing the drug, which are the nucleus for the chemical manufacture of some general pharmaceutical materials. The interest in medicinal plants has increased as antimicrobials, because of problems related to the use of antibiotics as resistance (Osungunna, 2020) [31], and through the results it was found that compination extracts were an inhibitory effect on the bacteria but with a different percentage and according to the type of the solvent used in extraction against the bacteria isolated, while the concentration of the extract was directly proportional to the rate of inhibition diameter, the highest inhibition was in concentration 400 mg/ml compared to the two concentrations 100 mg/ml and 200 mg/ml, and this is consistent with many studies that have prevent as in Voravuthikunchai, Rana and Rishan. Many of the chemical compounds present in the studied plants that were detected play an important role against pathogenic bacteria may be due to components that showed such as alkaloids, flavonoids, phenols, tannins, terpenes and saponins (Al-Sani, 2019) [6]. Alkaloids directly affect the nucleic acids present in the bacterial cell, in addition to working to block the formation of biofilms (Hodnik *et al.*, 2014) [17] The phenols that activate the enzymes responsible for major metabolic reactions by interfering with proteins, which lead to protein deformation and hence the inability of bacteria to grow. The reason may be that these plants possess flavonoids that are effective against bacteria because they contain carboxyl groups (-COOH) that deposit cell wall proteins and also contain one or more hydroxide groups (-OH), so these groups can bind proteins from during hydrogen bonds, which leads to the breaking of the cell wall, and thus the death of bacteria, Hussain is referred to in. Terpens have bacterial inhibitory activity because they work to rupture cellular membranes with lipophilic compounds. In addition to some vital saponins to participate in antimicrobial activity (Tiku, 2018) [37]. *L. nobilis* leaves extracts have different inhibitory effects on *P. aeruginosa*, *S. aureus* and *K. pneumoniae* isolated from patients with burns, This study is consistent with what confirmed by other authors have studied the antimicrobial activity of *L. nobilis* leaves hydroalcoholic extracts against several pathogens, showing interesting inhibitions against *K. pneumoniae*, *S. aureus* and *P. aeruginosa*, and with Cherrat *et al.* (2014) [11], they founds in *L.nobilis* leaf extracts compounds have antibacterial (Gram negative and Gram positive). As another study was conducted by Ratiba and Mohamed proving that the aqueous and alcoholic extracts contains more than one active substance and that some of these substances have an antimicrobial activity that exceeds that of known antibiotics. In 2016 Merghni *et al.* indicated that essential oils exhibited different anti-*staphylococcus* activities. The antimicrobial activities of *R. officinalis* were good against the pathogenic bacterial strains *P. aeruginosa* and *S. aureus*, as well as *K. pneumonia* (Jahani *et al.*, 2016) [21]. Bernardis *et al.* (2010) [9] showed effect of *R. officinalis* leaf extracts on the pathogenic bacteria present in the mouth, because it contained terpenes and polyphenols.In a recent study by Göksen indicated that this *R. officinalis* contains rich sources of biologically active compounds. The inhibitory cause of one or more of these substances may be attributed to their synergistic action, and among these compounds are phenolic compounds. *R. officinalis* leaves contains 1,8-cineole, α-pinene, rosmarinic acid, camphor, ursolic acid, carnosic acid and carnosol and limonene, these compounds act as antimicrobial agents. In addition to the other main components of essential oil, it has high antimicrobial activity against both Gram positive and Gram-negative bacteria. The essential oil works is a colorless or pale-yellow liquid that is a colorless or pale-yellow liquid against Gram positive and Gram-negative bacteria as well as against fungi because it contains camphor, α-pinene, borneol (Neves and Oliveira, 2018). Through previous studies and research on the effect of *Q. rubra* on bacteria, the reason for inhibition is its passion of phenolic acids, flavonoids and tannins compound (Skrypnik *et al.*, 2019) [36], which gave a stronger effect on the bacteria by has the ability to destroy cell membranes by forming complexes with proteins on the outer membrane of bacteria or by tearing the cell membranes by bonding with lipophilic substances present in the membrane as well, and this was confirmed by Ribechini. *Q. rubra* contains tannins it has antibacterial and anti-inflammatory properties. Pharmacological studies show the effectiveness of *Q. rubra* in purulent dermatitis (Dawid, 2013), also previous investigation revealed that extract of the *Q. rubra* consists of tannins and flavonoids, compounds (Vihakas, 2014) [38]. The constituents of *Q. rubra* comprise a large amount of tannins, gallic acid, ellagic acid, β-sitosterol, malic acid, chlorogenic acid and tannic acid (Rakić *et al.*, 2018) [34]. Their pharmacological effects were evaluated and found to be antibacterial. As for the effect of the mixture of three plant extracts on the studied bacteriaall aqueous and alcoholic extracts were effective with or higher than the results ofantibiotic inhibition, the hot water extract gave the highest inhibition rate against *P. aeruginosa* it was an approach with the result of Q. rubra. As for the alcoholic extract, n-hexane also had very good results, as it gave the highest rate of inhibition rate against S. aureus bacteria compared to the studied plants. When searching for local or foreign research or studies on the use of this mixture as an anti-bacterial, not find any indication of that, but there are a lot of studies on independent medicinal plants or mixed with other plants, and think the reason for this is that the plants in the mixture contain components effective and anti-bacterial, the synergistic action of these plants has given a high result in inhibition and this means that it possesses the material capable of killing bacteria and these active plant biological materials as previously described, have shared with each other alkaloids, flavonoids, phenols, tannins and terpenes, and their ability on breakthrough the cell's wall and the important structures exiting the cell and thus their death. Imipenem 10 mg was chosen, because the majority of bacteria could not resist it, most of which were sensitive to it, Imipenem the first of a new class of carbapenem antibiotics has activity against most Gram negative and Gram positive these are clinically important bacterial species. Also, this medicine may be especially useful in treating infections caused by bacteria mixtures (I El-Gamal and Oh, 2010) [20], effective methanol a proton polar solvents are distinguished by containing positively charged hydrogen ion and can be given to help dissolve and can solvent the most active substances found in the studied plants may be non-polar and polar (Johar *et al.*, 2015) [22]. n-hexane a non-polar solvent whose molecules consist of identical atoms in the electronegativity and can dissolve only non-polar molecules such as fatty acids (Ajeena, 2012) [1]. Polar solutions (polar solvents) such as water whose molecules are composed of asymmetric atoms in the electrical negativity can only dissolve the polar molecules (Khoshnood and Firoozabadi, 2015) [25]. Hot water extraction also gave high results, the reason is that some substances in plant tissues may need heat to melt and extract them (Houghton and Raman, 2012) [18] and showed by Uddin and Rauf. Upon reviewing a lot of research on the compounds fond in *L.nobilis*, *R.officianalis* and *Q.rubra* that are used as antimicrobials such as Difluoroheptacosanoic acid, rosmarinic acid, milbemycin and β-Sitosterol (Hussein *et al.*, 2016) [19], that among the most important substances is, which has been shown to have an effect of deactivation the cell membrane of bacteria such as *S. aureus* and *K.Pneumonia* by means of the quaternary amine group carried, that are present in the cell wall (Figueroa-Valverde *et al.*, 2009) [13] or they may combine with the polyamines that are bound DNA thus has a negative effect on cell proliferation and thus becomes effective against Gram negative and Gram positive bacteria (Polat *et al.*, 2011) [33].

Conclusion

Diverse medicinal properties, particularly antimicrobial activities. The study focuses on the antibacterial resistance found in burn patients, the results indicate that the plant extracts exhibit varying degrees of inhibition against common burn-associated pathogens, the antimicrobial efficacy of the extracts is solvent-dependent, with higher concentrations (400 mg/ml) showing more pronounced inhibitory effects. Notably, the combination of these three plant extracts showed enhanced antibacterial activity, likely due to a synergistic effect of their bioactive compounds. The study underscores the importance of further research into the synergistic effects of plant-based antimicrobial compounds for the development of novel therapeutic strategies.

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