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Dittrichia viscosa extracts' phytochemical screening, antibacterial, and synergistic effects against multi-resistant pathogenic microorganisms

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Introduction

When antibiotics were first used as a medicinal therapy in the 1940s, bacterial resistance to them emerged. To control the use of these medications, a number of alert strategies were introduced beginning in the 2000s. Consumption declined in response to these measures until 2010, but this decline was short-lived [1]. The widespread or insufficient use of antibiotics is linked to the problem of bacterial resistance, which may significantly raise the patient's risk of toxicity, expose side effects, result in medication interactions and super infections, or even cause death [2]. Therefore, it will be vital to look for therapeutic alternatives in order to reduce the harm and stop this issue from spreading. In fact, a number of recent studies have concentrated on the investigation of plant-based compounds that possess significant antibacterial properties, or the combination of these products with antibiotics to enhance their antibacterial properties. This study undoubtedly contributes to the hunt for neo-biomolecules to eradicate the emergence of multi-resistant bacterial strains.
The Dittrichia viscosa plant is characterized phytochemically in our work, and the antibacterial and synergistic efficacy of its aqueous and ethanolic extracts against pathogenic bacteria that are resistant to many drugs is assessed.

Materiel and Methods Plant material

Dittrichia viscosa, often known as inul, is a wild perennial plant coated in glandular hairs that exude a sticky, camphor-like resin. It is distinguished by a taproot and a depth of roughly 1.50 meters. This species has densely foliaged, highly branching stems that are immediately inserted without petioles. As it ages, its alternating, elongated to lanceolate leaves turn woody and black at the base. The flowers are arranged in heads, either with orange-yellow tubes or petals welded in yellow tabs [3].Plant preparation and harvesting
In May 2016, D. viscosa leafy stems were physically harvested from the outskirts of Oued Rdoum to Sidi Kacem (Latitude: 34.221 °, Longitude: -5.707) in Morocco.
The Plant Biotechnology and Molecular Biology Laboratory of Moulay Ismail University's Faculty of Science in Meknes has identified the species [4]. After sorting, this plant material was allowed to dry at ambient temperature in the shade. Following drying, a fine powder is produced by electric grinding, which is then utilized to prepare the extracts.

Bacterial strains examined
Five harmful microorganisms were used to test the antibacterial activity of D. viscosa preparations. CNRST's Laboratory of Microbiology and Molecular Biology (LMBM) supplied Listeria monocytogenes, while four were clinically isolated from various pathological products of a Private Medical Analysis Laboratory. They were removed and isolated using the proper selective culture media and in compliance with the current hygienic regulations [5].
The strains that were examined are:
Methicillin-resistant Staphylococcus aureus (MRSA) and Listeria monocytogenes are examples of cocci and bacillus

Gram (+).
• Bacilles Gram (-): Salmonelle sp., Pseudomonas aeruginosa, and Klebsiella pneumoniae.
Methods used to prepare the plant extracts
The powdered leafy stems of D. viscosa were used to make two different types of extracts: ethanolic and aqueous.

One liter of distilled water is used to boil one hundred grams of the plant's vegetable for fifteen minutes. This 10% cooled decoction was filtered sequentially through Wattman paper N° 1 and hydrophilic cotton. After that, the filtrate was placed in an oven set at 55 °C until it had dried. The residue is diluted in water to achieve specified concentrations, which are given in milligrams per milliliter.

• An ethanolic extract

By macerating 100 g of the vegetable powder in 300 ml of ethanol for 24 hours, the ethanolic extract is produced at room temperature with magnetic stirring. After that, the extract is filtered through Wattman paper No. 1 and hydrophilic cotton. To remove ethanol and obtain a dry residue measured in milligrams, the collected filtrate is dried in an oven set at 50 degrees Celsius. This residue is diluted in dimethyl sulfoxide (DMSO) to create various concentrations, which are then measured in milligrams per milliliter.

Screening using phytochemicals
It is a method for identifying the various chemical groups present in a plant organ that is based on a series of physicochemical reactions. To comprehend the functions and impacts of plants, this research is crucial. Alkaloids, polyphenols (flavonoids, anthocyanins, and tannins), saponosides, steroids, sterols, and triterpenes are the primary phytochemical groups that were highlighted in this phytochemical study, which was realized through reactions in solution in test tubes in accordance with the Diallo [6] protocol.

Antibacterial activity research and inoculum preparation

The inoculum is made from an 18–24 hour bacterial culture that is produced on agar medium and incubated at 37 °C. Several colonies of the same morphology are then suspended in saline using a cotton swab or a sterile loop. must possess an inoculum that is as dense as the Mc Farland Standard 0.5 [5].
• The minimal inhibitory concentration (MIC) is determined.
MIC is the lowest extract concentration that, after 18 to 24 hours of incubation at 37 °C, prevents 90% of the bacterial population from growing. The microtitration method on microplates outlined by Ennacerie and his associates is used to determine the MICs of the plant extracts in relation to the bacterial strains [7, 8, 9]. Following incubation, each well receives an addition of [2, 3, 5]-triphenyl-2H-tetrazolium chloride (TTC), a bacterial viability indicator. Pink coloration is seen in wells where bacterial growth has taken place.
Without adding the extract, the growth controls are made in separate wells with the culture media and the tested bacterial strains. Three repetitions are required for every test that is administered.

• Calculating the MBC, or minimum bactericidal concentration
The lowest concentration of a drug that leaves at most 0.01% of surviving germs is known as the minimum bactericidal concentration, or MBC. It is ascertained by adhering to the procedure mentioned by Yao and his associates [10, 11]. In three consecutive experiments, each experiment is conducted three times.
The antibacterial impact can be assessed using the CMB/MIC ratio; if the ratio is less than 4, the effect is bactericidal; if it is greater than 4, the effect is bacteriostatic [12, 13].

Antibiotics and extracts have synergistic antibacterial interactions: The disk diffusion method
Using this method, the impact of the extracts and antibiotics to which the tested bacteria are resistant is assessed. Two

antibiotics to which the strain is resistant are tested for each strain. In accordance with the procedure outlined by Ennacerie and his associates, the test is conducted on a solid media [9,14,15]. Depending on the kind of aqueous or ethanolic extract, a disk impregnated with distilled water or DMSO is used to present the negative test.
There are four primary ways that the antibiotic and extract can interact: Indifference: the extract's activity has no effect on the antibiotic's activity; addition: the effect of the association is equal to the sum of the effects produced by each of the agents taken separately; synergy: the effect of the association is greater than the sum of the effects produced by each of the agents taken separately; and antagonism: the effect of the combination is less than the sum of the effects produced by each of the antibiotics taken separately [15].

Findings and Conversation
Screening using phytochemicals
The data described in Table 1 were obtained by an initial assessment of the phytochemical content of the leafy stems of the D. viscosa plant.

Groups of compounds	Classes	*D. viscosa*
Nitrogen compounds	Alkaloids	-
	Tannins	+++
	Gallic Tannins	+++
	Catechetical Tannins	-
Polyphenolic compounds	Free Flavonoids	++
	Anthocyanins	-
	Leucoanthocyanins	-
Terpene compounds	Steroids	-
	Sterols and triterpenes	++
	Saponosides (Foam index)	*100*

Table 1: Results of characterization reactions of chemical groups in leafy stems of *D. viscosa* plants.
The saponoside characterization is carried out by determining the height of the foam formed in the tubes.
+ + + +: Frankly positive reaction; + + +: Positive reaction; + +: Reaction moderately positive; + : Shady reaction; - : Negative reaction.

Phytochemical screening allowed us to highlight the presence of secondary metabolites in the plant tissues of the studied plant. The detection of these chemical compounds is based on tests of constituent solubilities, precipitation and turbidity reactions, and a specific color change.

In fact, *Dittrichia viscosa* leafy stems contain gallic tannins, flavonoids, saponosides, sterols and triterpenes, and they lack alkaloids, steroids, anthocyanins and leucoanthocyanins. Referring to previous studies conducted by Boumaza in Algeria, we note a similarity in results concerning the presence of tannins, flavonoids, saponosides, sterols and triterpenes, but a difference for anthocyanins that are absent in our case [16]. Other studies have identified the phytochemistry of the aerial part of the same plant, they revealed that it contains flavonoids, sesquiterpene acids and triterpenes esters [17]. According to Cohen et al. [18] *D. viscosa* leaves also contain phenolic compounds, terpenoids and sesquiterpene lactones. The difference in chemical composition is directly related to climatic and soil factors, as well as the physiological characteristics of the plant.

Antibacterial activity of *D. viscosa* extracts

The profile of antibiotic resistance bacteria tested **(Table 2)**, revealed a high resistance level for the majority of antibiotics prescribed currently in antibiotherapy [19].

Antibiotic disc	Disc load	*SARM*	*Listeria monocytogenes*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Salmonella sp*
Ampicillin	10 µg	NT	R	NT	NT	R
Amoxicillin	25µg	NT	NT	R	NT	NT
Amoxicillin + Clavulanic acid	20/10µg	NT	NT	R	NT	NT
Penicillin G	6 µg	NT	S	NT	NT	NT
Ceftriaxone (C3G)	30 µg	S	NT	S	NT	S
Ceftazidime (C3G)	30 µg	NT	NT	R	R	S
Ticarcillin	75 µg	NT	NT	RN	R	NT
Imipenem	10 µg	NT	NT	NT	R	NT
Oxacillin	5 µg	R	NT	NT	NT	NT
Meropenem	30 µg	NT	S	NT	NT	NT
Gentamycin	15 µg	S	NT	S	S	S
Ciprofloxacin	5 µg	R	NT	R	R	S

Ofloxacin	5 µg	R	NT	S	S	NT
Sulphamethoxazol + Trimethoprim	1,25/23,75 µg	R	S	R	S	S
Doxycycline	30 µg	S	NT	R	NT	NT
Erythromycin	15 µg	R	S	NT	NT	NT
Streptomycin	300µg	NT	NT	NT	NT	R
Colistin sulfate	50µg	NT	NT	NT	NT	R
Ceftriaxone	30 µg	NT	NT	NT	NT	S
Tetracycline	30µg	NT	NT	NT	NT	S
Cefamandole		NT	NT	NT	NT	S
Chloramphenicol	30 µg	NT	NT	NT	NT	S
Kanamycin	30µg	NT	NT	NT	NT	S

Table 2: Antibiotic resistance profile of tested bacteria.*SARM:* *Staphylococcus aureus* resistant to methicillin.
(-): Not determined **NT**: Not tested

The antibacterial effect of the two aqueous and ethanolic extracts prepared from the leafy stems of *D. viscosa* on the five strains tested is reported in **Table 3**.

The results of the antibacterial activity reveal that the MICs of the two aqueous and ethanolic extracts range from 0.858 ± 0.29 to 66.66 ± 0.00 mg / ml with a strong activity for the alcoholic extract. The latter showed a stronger inhibition of bacterial growth against Gram-negative than Gram-positive strains. While the decoction generally has the same lower activity against both types of Gram is a MIC of 33.33 ± 0.00 mg / ml, xcept for *Pseudomonas aeruginosa* where the MIC is 66.66 ± 0.00 mg / ml.

Regarding MBC, **Table 3** shows that decoction 10% does not cause any *D. viscosa* has a bactericidal effect against both Gram-positive germs, MRSA and *Listeria monocytogenes*, moderately bactericidal against *Salmonella* sp and *Pseudomonas aeruginosa* and a bacteriostatic effect against *Klebsiella pneumoniae*

Extracts		**Gram -**			**Gram +**	
		Klebsiella pneumoniae	***Salmonelle sp***	***Pseudomonas aeruginosa***	**SARM**	***Listeria monocytogenes***
Ethanolic extract	**MIC**	1,425 ±0,40	2,423 ±0,55	0,858± 0,29	1,425±0,43	3,096±0,71
	MBC	11,610±2,31	10,2±1,16	4,300±1,01	4,583±0,41	9,16±0,12
	MBC/MIC	>4	≥4	≥4	<4	<4
Decocted 10%	**MIC**	33.33±0,00	33,33±0,00	66,66±0,00	33.33±0,00	33.33±0,00
	MBC	-	-	-	-	-
	MBC/MIC	-	-	-	-	-

(-) : Indeterminate
MRSA: Methicillin-resistant *Staphylococcus aureus*.

Table 3: Antibacterial Activity Evaluated by Minimal Inhibitory Concentration (MIC) and Minimal Bactericidal Concentration (MBC) Expressed in mg / ml and the CMB/MIC of Extracted Leaf Stems of *D. viscosa*

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Regarding MBC, **Table 3** shows that decoction 10% does not cause any lethal effect on the five strains tested. However, the ethanolic extract has MBCs ranging from 4.300 ± 1.01 to 11.610±2.31 mg / ml. Based on the MBC / MIC ratio, it is clear that the alcoholic extract of *D. viscosa* has a bactericidal effect against both Gram-positive germs, MRSA and *Listeria monocytogenes*, moderately bactericidal against *Salmonella* sp and *Pseudomonas aeruginosa* and a bacteriostatic effect against *Klebsiella pneumoniae*.

		Diameters of the inhibition zones (mm)		
			Combined extract with antibiotics	
Bacterial Strain	**Antibiotic Code and Critical Diameter**	**Antibiotic Alone**	**Ethanol Extract**	**Decocted 10%**
SARM	**(Extract alone)**		*23*	*7*
	E<18	*8*±0.00	*6*	***40***
	CN <18	17.33±0.88	*15*	*6*
Listeria monocytogenes	**(Extract alone)**		*19.5*	*8.5*
	E<25	*7±0.00*	***30***	*14*
	P<13	7±0.00	***40***	*13*
Klebsiella pneumoniae	**(Extract alone)**		*37*	*7.8*
	CRO<23	16±3.66	*7*	*6*
	C<20	11.5±0.5	*0*	*10*
Pseudomonas aeruginosa	**(Extract alone)**		*25*	*6*
	AK<15	14.5±0.44	*15*	*14*
	IMP<17	12±0.00	***38***	***24***
Salmonelle sp	**(Extract alone l)**		*35*	*7.5*
	CTX<23	10±0.00	*8*	*10*
	CT<15	13±0.66	*10*	*13*

Table 4: Combination effect extracted from *D. viscosa* / antibiotic against five bacterial strains.

MRSA: Methicillin-resistant *Staphylococcus aureus*
P : Pénicilline (10 Unités), **CN** : Gentamicine (10µg), **E** : Erythromycine (15µg), ***CRO*** : Ceftriaxone (30µg), ***C*** : Chloramphénicol (30µg), **IMP** : Imipénème (10µg), **CTX** : Cefotaxime (30µg), **CT** : Colistine (50µg), **AK** : Amikacine (30µg)

Of the 20 combinations, 15 showed an antagonistic effect by reduction of inhibition diameter. While five combinations allowed the amplification of the antibacterial power of antibiotics from a percentage of 75 to 471%. This synergistic effect is recorded for three antibiotics, Penicillin and Imipenem from the beta-lactam family and Erythromycin from the Macrolide family against three resistant strains MRSA, *Listeria monocytogenes* and *Pseudomonas aeruginosa*.The analysis of these results shows that the two types of extract can improve the antibacterial power of antibiotics during their association. However, the explanation of this amplifying effect requires in-depth studies that aim to elucidate the detailed mode of action of the active ingredients of each extract on pathogenic bacteria. However, this component is still poorly illustrated.

Referring to the results of other research, that of Side Larbi and his collaborators [22] treating extracts of *D. viscosa*, they found a synergistic effect of 77% in the case of the association of the methanolic extract of this species harvested from Algeria, with Gentamicin against *E. coli*.

This synergism between antibiotics and extracts is generally related to the destabilization of the bacterial wall. Indeed, it can be assumed that the components of the extracts facilitate the penetration of antibiotic molecules and thus their access to their intracellular targets.

More particularly, according to Esimone et al. [23] polyphenols coupled with β-lactams can enhance antibacterial activity by disrupting cell membrane transpeptidation. As for the combination of imipenem with extracts, it promotes membrane permeability and makes it easier for antibiotic molecules to reach their intracellular target while helping stop bacterial growth. For Macrolides, their association with biologic agents

can inhibit bacterial overgrowth by reversible binding to the bacterial ribosome 50s subunit, which can prevent transpeptidation and translocation reactions, resulting in synthesis of RNA-dependent proteins [24,25].

Taking into account the results of the antibacterial activity of *D. viscosa* extracts against *P. aeruginosa* resistant to imipenem, it was noted that the aqueous extract was not effective for the inhibition of its growth compared to the ethanol extract and whose explanation can be attributed to the texture of the wall of this bacterium which is provided with an outer membrane rich in phospholipid and forming a barrier impermeable to hydrophobic molecules [26]. In addition, its resistance to imipenem is due to a loss of porin D2 causing a decrease in its permeability, and a production of chromosomal céphalosporinase [27]. The combination of the two extracts with imipenem has produced a restoration of the sensitivity of this strain by an improvement of more than 100% of the antibacterial power of this antibiotic. The inhibitory effect of the growth of this bacterium is most likely due to the creation of porosity and an increase in cell permeability in favor of antibiotic entry. As it can be explained by the breaking of other mechanisms of resistance of this germ. In addition, this surprising result in restoring the weakened efficacy of imipenem on *P. aeruginosa*, an opportunistic and multidrug-resistant pathogen that is constantly evolving, is a promising and promising addition to antibiotic therapy that is currently therapeutic impasse for certain bacterial strains.

L. monocytogenes, also revealed this synergistic effect with the two antibiotics erythromycin and penicillin whose maximum amplification is evaluated at 471%. The wall of this strain is characterized by a low content of phospholipids hence the ease of contact of the phospholipid

bacterial membrane bilayer with hydrophobic substances. This element could be the cause of ion leakage, enzymatic system failure, or the loss of essential intracellular components [28], which would increase the antibiotic's growth inhibitory effect.
One approach that can offer therapeutic and socioeconomic answers is to assess the impact of extract/antibiotic combinations. It is a chance to restore the efficacy of antibiotics that have been compromised by the development of various resistances. Additionally, it helps combat infectious diseases that are incurable and lowers the cost of infection medications, which are typically costly.
Antibiotic therapy is not the only field that is interested in results; the food, cosmetic, and pharmaceutical sectors can all benefit greatly from them.

In conclusion

Given their intriguing effects on multi-resistant pathogenic bacteria, it can be said that the two extracts of the medicinal plant D. viscosa are rich in active chemicals. Additionally, their antibacterial efficacy was enhanced when combined with beta-lactam and macrolide antibiotics.
Therefore, these extracts may include bioactive compounds that can be separated and used as adjuvants to antibiotics to combat these infections.

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