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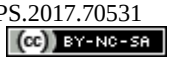
ISSN 2231-3354 

Combination evaluation of some Algerian medicinal plant extracts in association with antibiotics

Mohamed Senouci Bereksi[1*], Hafida Hassaïne[2], Djamel Eddine Abdelouahid[2]

[1]Natural Products Research Laboratory (LAPRONA), Department of Biology, University of Tlemcen, 13000 Tlemcen, Algeria.
[2]Laboratory of Applied Microbiology in Food, Biomedical and Environment (LAMAABE), Department of Biology, University of Tlemcen, 13000 Tlemcen, Algeria.

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ABSTRACT

In vitro antibacterial activity of hydromethanolic extracts of nine Algerian medicinal plants were evaluated alone and in combination with five antibiotics against six Gram-positive and Gram-negative pathogenic bacteria: *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, using well diffusion method. The extracts of plant tested, with the exception of *Cassia angustifolia*, *Nigella sativa* and *Zingiber officinale*, showed different levels of antibacterial activities against most pathogens with diameters varying from 06.0 to 25.0 mm, especially against *S. aureus*. Combinations of plant extracts and antibiotics showed different synergistic effects resulting in increased areas of inhibition of some antibiotics combined with plant extracts, including those presented weak antibacterial activity. The tested extracts could be used in combination therapy as a source of resistance modifying agents for the treatment of infections caused by pathogenic bacteria.

INTRODUCTION

One of the central themes of success in human therapeutics in the 20th century was the discovery and development of antibiotics and antibacterial agents, for the treatment of bacterial infections. A huge array of antibacterial agents has been introduced and antibiotics can be used effectively to treat major infectious diseases (Wood, 1990). However, the usage of antibiotics and antibacterial chemotherapeutics is becoming more and more restricted, because bacteria is capable of developing resistance to antibiotics soon after their introduction and most antibiotics have side effects. Therefore, it becomes essential to search for newer drugs with lesser rate of resistance development and lesser toxicity (Okeke *et al*., 2005).

Phytomedicines derived from plants have shown great promise in the treatment of intractable infectious diseases including viral infections (Cowan, 1999). Single and poly herbal preparations have been used numerously throughout history for the treatment of various diseases (Abu-Shanab *et al*., 2004). In rational drug therapy, the concurrent administration of two or more drugs is often essential and sometimes mandatory in order to achieve the desired therapeutic goal or to treat co-existing diseases (Levinson and Jawetz, 2002).

Many researchers have studied experimentally the synergistic effect resulting from the combination of antibiotics with different plant extracts (Aburjai *et al*., 2001; Aqil *et al*., 2005; Olajuyigbe and Afolayan, 2012). Indeed, this combination therefore allowed reducing bacterial resistance to drugs (Abascal and Yarnell, 2002).

* *Corresponding Author*
Mohamed Senouci Bereksi, Mailing address: Natural Products Research Laboratory (LAPRONA), Department of Biology, University of Tlemcen, 13000 Tlemcen, Algeria. Tel.: +213-793-282-503
Email: sbereksi_mohamed @ yahoo.fr

Thousands of species of wild herbs growing in Algeria and whose medicinal properties have been appreciated for millennia by the inhabitants belong to the most modest and domestic plants, containing substances of preventive and curative diseases (Belouad, 2001). Some Algerian plants exhibit significant potency against human bacteria (Mezouar *et al*., 2014; Selaadji *et al*., 2014), but few of them have been devoted to the study of combined effects between plants and chemical antimicrobials (Ghellai *et al*., 2014).

The aim of this study is to evaluate *in vitro* antibacterial activities of hydromethanolic extracts from nine Algerian medicinal plants and to study the possible synergistic effect of the combination of these extracts with some antibiotics against six standard bacterial strains by using the well diffusion method.

MATERIAL AND METHODS

Plant materials

Samples of *Cistus monspeliensis* (aerial part), *Punica granatum* (fruit peels) and *Withania frutescens* (leaves) were collected from Tlemcen (West of Algeria) and *Rhus tripartita* (aerial part) was collected in the region of Bechar (South of Algeria), in March 2013. They were identified in the Laboratory of Natural Products, Department of Biology, University of Tlemcen, Algeria. Voucher specimens were deposited at the Herbarium of the Laboratory.

The plants were dried at room temperature for two weeks. While *Berberis vulgaris* (root bark), *Cassia angustifolia* (leaves), *Cinnamomum cassia* (peels), *Nigella sativa* (seeds) and *Zingiber officinale* (rhizome) were purchased from local market in Tlemcen, Algeria in the same period.

Preparation of plant extracts

Air dried material of each species was ground and submitted for extraction. 10 g of the dry plant powder of each plant was macerated with 100 ml of methanol/water (80:20, v/v) overnight at room temperature under constant shaking. The extracts were then filtered and concentrated under reduced pressure at 45 °C using rotary evaporator (Hahnvapor, Hahn Shin Scientific, South Korea).

Then, the dry residues were dissolved in Dimethylsulfoxid (DMSO) to a final concentration of 100 mg/ml and filtered by 0.45 µm Millipore filters for sterilization before used.

Bacterial strains

Six bacterial strains were used in this study, *Staphylococcus aureus* (ATCC 29213), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922), *Entrobacter cloacae* (ATCC 13047), *Klebsiella pneumoniae* (ATCC 700603) and *Pseudomonas aeruginosa* (ATCC 27853). Usually, these strains are the most common Gram positive and Gram negative bacteria found in nosocomial infections (Kaoutar *et al.*, 2004). Bacterial strains were grown on nutrient agar slants for 24 h at 37 °C then used in the experiments.

Antibiotics

Plant extracts of the current study were evaluated for synergism assay with five antibiotics (Amoxicillin, Ceftazidim, Ceftriaxon, Cefotaxim and Cefazolin) which were diluted to a final concentration of 1000 µg/ml.

Determination of antibacterial activity and synergistic effect

Antibacterial activity was measured by well diffusion method according to the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standard) (NCCLS, 1993). Briefly, plates containing approximately 25-30 ml of Mueller Hinton agar medium were inoculated using a cotton swab with a 18-24 h old culture of the bacterial strains. Wells (6 mm diameter) were punched in the agar and filled with 30 µl of plant extracts or antibiotics. The plates were incubated at 37°C for 18-24 h. The antibacterial activity was assessed by measuring the inhibition zone diameter (mm) around the well.

Synergism effect was evaluated using the previous method. The wells were filled with 30 µl of antibiotic and 30 µl of plant extract (Adwan *et al*., 2008). An increase in growth inhibition zone indicates a synergistic effect (Ahmed *et al*., 2007).

RESULTS AND DISCUSSION

Antibacterial activities of hydromethanolic extracts of nine medicinal plants and their combinations with antibiotics were assayed *in vitro* by the well diffusion method against six standard Gram-positive and Gram-negative pathogenic bacteria (Tables 1, 2, 3, 4, 5, 6). It can be noted that most of antibiotics showed different levels of antibacterial activity against different bacterial strains. All the tested bacteria were more or less sensitive to the plant extracts. The plant extracts, except those of *Cassia angustifolia* and *Zingiber officinale*, showed the most important antibacterial activity against *S. aureus* with diameters of the zones of inhibition varying from 09.0 to 25.0 mm. We can note that this activity is much more pronounced by *Berberis vulgaris*, *Cinnamomum cassia*, *Cistus monspeliensis*, *Punica granatum* and *Withania frutescens* with diameters of the zones of 25.0, 15.0, 18.0, 22.0 and 17.0 mm respectively (Table 1). This high activity may be due to the composition of these extracts with compounds which may be responsible for this activity. Indeed, plants are rich in a variety of phytochemicals including tannins, terpenoids, alkaloids, and flavonoids which have been found in vitro to have antimicrobial properties (Dorman and Deans, 2000; Talib and Mahasneh, 2010).

For the other bacterial species, only the extracts of *C. cassia*, *C. monspeliensis* and *P. granatum* showed a moderate activity with diameters varying from 09.0 to 11.0 mm (Tables 2, 3, 4, 5, 6). However, these plants gave appreciable activity (diameters of 12.0, 14.0 and 15.0 mm respectively) against

Table 1: Antibacterial activity of plant extracts and synergistic effects with antibiotics on *Staphylococcus aureus* (mm).

Plant	Extracts alone	Antibiotics (alone/combined with extracts)				
		AMX	CAZ	CRO	CTX	CZ
		46.0	24.0	25.0	30.0	41.0
➢ *Berberis vulgaris*	25.0	44.0 A	25.0 I	26.0 I	34.0 S	38.0 A
➢ *Cassia angustifolia*	-	46.0 I	22.0 A	26.0 I	32.0 S	40.0 A
➢ *Cinnamomum cassia*	15.0	42.0 A	21.0 A	26.0 I	30.0 I	36.0 A
➢ *Cistus monspeliensis*	18.0	46.0 I	21.0 A	28.0 S	32.0 S	37.0 A
➢ *Nigella sativa*	09.0	40.0 A	21.0 A	25.0 A	31.0 I	37.0 A
➢ *Punica granatum*	22.0	46.0 I	24.0 I	28.0 S	32.0 S	40.0 I
➢ *Rhus tripartita*	12.0	40.0 A	22.0 A	22.0 A	28.0 A	43.0 S
➢ *Withania frutescens*	17.0	48.0 S	22.0 A	23.0 A	29.0 A	45.0 S
➢ *Zingiber officinale*	-	40.0 A	22.0 A	24.0 A	31.0 I	43.0 S

- : No inhibition zone observed, AMX : Amoxicillin, CAZ : Ceftazidim, CRO : Ceftriaxon, CTX : Céfotaxim, CZ : Céfazolin, S : Synergy, A : Antagonism, I : Indifference.

Table 2: Antibacterial activity of plant extracts and synergistic effects with antibiotics on *Enterococcus faecalis* (mm).

Plant	Extracts alone	Antibiotics (alone/combined with extracts)				
		AMX	CAZ	CRO	CTX	CZ
		13.0	40.0	39.0	38.0	-
➢ *Berberis vulgaris*	-	12.0 A	42.0 S	36.0 A	36.0 A	-
➢ *Cassia angustifolia*	-	13.0 I	39.0 A	36.0 A	36.0 A	-
➢ *Cinnamomum cassia*	12.0	12.0 A	39.0 A	36.0 A	36.0 A	11.0 A
➢ *Cistus monspeliensis*	09.0	10.0 A	38.0 A	35.0 A	36.0 A	09.0 I
➢ *Nigella sativa*	-	16.0 S	39.0 A	36.0 A	36.0 A	-
➢ *Punica granatum*	11.0	11.0 A	38.0 A	36.0 A	37.0 A	10.0 A
➢ *Rhus tripartita*	-	12.0 I	36.0 A	34.0 A	35.0 A	-
➢ *Withania frutescens*	-	12.0 I	42.0 S	45.0 S	35.0 A	-
➢ *Zingiber officinale*	-	13.0 I	39.0 A	37.0 A	36.0 A	-

- : No inhibition zone observed, AMX : Amoxicillin, CAZ : Ceftazidim, CRO : Ceftriaxon, CTX : Céfotaxim, CZ : Céfazolin, S : Synergy, A : Antagonism, I : Indifference.

Table 3: Antibacterial activity of plant extracts and synergistic effects with antibiotics on *Escherichia coli* (mm).

Plant	Extracts alone	Antibiotics (alone/combined with extracts)				
		AMX	CAZ	CRO	CTX	CZ
		20.0	33.0	33.0	36.0	24.0
➢ *Berberis vulgaris*	-	17.0 A	30.0 A	33.0 I	35.0 A	21.0 A
➢ *Cassia angustifolia*	-	16.0 A	30.0 A	32.0 A	37.0 I	21.0 A
➢ *Cinnamomum cassia*	11.0	18.0 A	30.0 A	34.0 I	38.0 S	22.0 A
➢ *Cistus monspeliensis*	11.0	11.0 A	30.0 A	32.0 A	36.0 I	22.0 A
➢ *Nigella sativa*	-	17.0 A	31.0 A	32.0 A	36.0 I	21.0 A
➢ *Punica granatum*	10.0	10.0 A	32.0 A	33.0 I	40.0 S	21.0 A
➢ *Rhus tripartita*	09.0	12.0 A	32.0 A	31.0 A	35.0 A	24.0 I
➢ *Withania frutescens*	-	20.0 I	32.0 A	31.0 A	34.0 A	24.0 I
➢ *Zingiber officinale*	-	19.0 A	32.0 A	32.0 A	35.0 A	24.0 I

- : No inhibition zone observed, AMX : Amoxicillin, CAZ : Ceftazidim, CRO : Ceftriaxon, CTX : Céfotaxim, CZ : Céfazolin, S : Synergy, A : Antagonism, I : Indifference.

P. aeruginosa, which is known for it increased resistance to various antimicrobial agents. According to the literature, the difference in sensitivity between Gram positive and Gram negative bacteria can be ascribed to morphological differences between these microorganisms, above all to differences in the permeability of the cell wall (Nastro *et al.*, 2000). Antimicrobial combinations are used for a number of reasons: expansion of antimicrobial spectrum, minimization of drug toxicity, minimization of antimicrobial resistance, and antimicrobial synergism (Verma, 2007). Combinations between the extracts of the studied plants and the antibiotics tested showed different effects of synergy or indifference, while other interactions presented an antagonism against the different bacterial strains tested. For the *S. aureus* strain, a synergistic effect was observed between cefotaxim and extracts of *B. vulgaris* and *C. angustifolia*, and also between cefotaxim and ceftriaxon with the extracts of *C. monspeliensis* and *P. granatum*. Simultaneously, cefazolin presented a synergy with *R. tripartita*, *W. frutescens* and *Z. officinale* extracts, and also amoxicillin when combined with *W. frutescens* (Table 1). From Table 2, we note a synergism between amoxicillin, ceftazidim and ceftriaxon when they were combined with *B. vulgatis*, *N. sativa* and *W. frutescens* respectively, against *E. faecalis*. In parallel, *C. cassia* and *P. granatum* showed synergistic interactions against *E. coli* when combined with cefotaxim (Table 3).

A synergistic effect was also observed in *E. cloacae* (Table 4) when combinations between amoxicillin and cefazolin and extracts of *C. cassia, C. monspeliensis* and *R. tripartita* were applied. No synergistic effect was detected in the combination of all plant extracts with the antibiotics tested against *K. pneumoniae*. However, we note an interaction leading to a synergistic effect between amoxicillin and the extract of *C. cassia* against *P. aeruginosa* (Tables 5, 6).

Table 4: Antibacterial activity of plant extracts and synergistic effects with antibiotics on *Enterobacter cloacae* (mm).

Plant	Extracts alone	Antibiotics (alone/combined with extracts)				
		AMX	CAZ	CRO	CTX	CZ
		-	32.0	32.0	35.0	-
➢ *Berberis vulgaris*	-	-	30.0 A	31.0 A	36.0 I	-
➢ *Cassia angustifolia*	-	-	30.0 A	32.0 I	33.0 A	-
➢ *Cinnamomum cassia*	09.0	12.0 S	30.0 A	32.0 I	34.0 A	16.0 S
➢ *Cistus monspeliensis*	-	09.0 S	30.0 A	32.0 I	33.0 A	10.0 S
➢ *Nigella sativa*	-	-	31.0 A	31.0 A	34.0 A	-
➢ *Punica granatum*	10.0	11.0 I	28.0 A	28.0 A	34.0 A	11.0 I
➢ *Rhus tripartita*	-	11.0 S	31.0 A	28.0 A	32.0 A	08.0 S
➢ *Withania frutescens*	-	-	30.0 A	30.0 A	32.0 A	-
➢ *Zingiber officinale*	-	-	33.0 I	29.0 A	32.0 A	-

- : No inhibition zone observed, AMX : Amoxicillin, CAZ : Ceftazidim, CRO : Ceftriaxon, CTX : Céfotaxim, CZ : Céfazolin, S : Synergy, A : Antagonism, I : Indifference.

Table 5: Antibacterial activity of plant extracts and synergistic effects with antibiotics on *Klebsiella pneumoniae* (mm).

Plant	Extracts alone	Antibiotics (alone/combined with extracts)				
		AMX	CAZ	CRO	CTX	CZ
		-	22.0	26.0	30.0	11.0
➢ *Berberis vulgaris*	-	-	21.0 A	23.0 A	29.0 A	11.0 I
➢ *Cassia angustifolia*	-	-	21.0 A	24.0 A	29.0 A	12.0 I
➢ *Cinnamomum cassia*	10.0	11.0 I	22.0 I	25.0 A	28.0 A	11.0 I
➢ *Cistus monspeliensis*	10.0	10.0 I	21.0 A	24.0 A	28.0 A	09.0 A
➢ *Nigella sativa*	-	-	21.0 A	24.0 A	28.0 A	10.0 A
➢ *Punica granatum*	11.0	10.0 A	20.0 A	24.0 A	28.0 A	09.0 A
➢ *Rhus tripartita*	-	-	14.0 A	25.0 A	28.0 A	10.0 A
➢ *Withania frutescens*	-	-	22.0 I	27.0 I	30.0 I	09.0 A
➢ *Zingiber officinale*	-	-	21.0 A	25.0 A	28.0 A	11.0 I

- : No inhibition zone observed, AMX : Amoxicillin, CAZ : Ceftazidim, CRO : Ceftriaxon, CTX : Céfotaxim, CZ : Céfazolin, S : Synergy, A : Antagonism, I : Indifference.

Table 6: Antibacterial activity of plant extracts and synergistic effects with antibiotics on *Pseudomonas aeruginosa* (mm).

Plant	Extracts alone	Antibiotics (alone/combined with extracts)				
		AMX	CAZ	CRO	CTX	CZ
		-	36.0	28.0	27.0	-
➢ *Berberis vulgaris*	-	-	34.0 A	25.0 A	25.0 A	-
➢ *Cassia angustifolia*	-	-	35.0 A	24.0 A	23.0 A	-
➢ *Cinnamomum cassia*	12.0	14.0 S	33.0 A	25.0 A	24.0 A	13.0 I
➢ *Cistus monspeliensis*	14.0	14.0 I	36.0 I	25.0 A	26.0 A	12.0 A
➢ *Nigella sativa*	-	-	34.0 A	22.0 A	23.0 A	-
➢ *Punica granatum*	15.0	16.0 I	35.0 A	24.0 A	24.0 A	16.0 I
➢ *Rhus tripartita*	-	-	33.0 A	24.0 A	25.0 A	-
➢ *Withania frutescens*	-	-	33.0 A	23.0 A	25.0 A	-
➢ *Zingiber officinale*	-	-	34.0 A	25.0 A	24.0 A	-

- : No inhibition zone observed, AMX : Amoxicillin, CAZ : Ceftazidim, CRO : Ceftriaxon, CTX : Céfotaxim, CZ : Céfazolin, S : Synergy, A : Antagonism, I : Indifference.

Our results are in agreement with previous works on combinations of antimicrobial agents with different plant extracts which reported synergistic effects against different resistant bacteria (Ahmed and Aqil, 2007; Aiyegoro *et al*., 2009; Horiuchi *et al.*, 2007; Nascimento *et al*., 2000) and stand out as veritable sources of potential resistance modifying agents (Sibanda and Okoh, 2007). For the rest of combinations, although some of plant extracts showed weak antibacterial activity, they exhibited either indifference or antagonistic effects on different tested bacterial strains. This could be attributed to the inability of higher concentrations of plant extracts to diffuse through the agar medium. This impairment in drug diffusion is a major limitation in the evaluation of the antimicrobial effects of plant extracts using the agar diffusion method (Esimone *et al*., 2006). We can note that the synergism recorded here to plant extracts with weak action on different tested bacterial strains, such as *C. angustifolia*, *N. sativa* and *Z. officinale*, is an important data since they showed a synergism profile similar to that of *B. vulgaris, C. monspeliensis* and *P. granatum* extracts, considered the most active tested plant extracts in this study. Thus, certain authors suggest that the researchers should investigate the synergistic capacity of plant extracts or other natural products; independent of the antimicrobial activity they have (Betoni *et al*., 2006). A number of *in vitro* studies have reported the use of plant extracts in combination with antibiotics, showing significant reduction in the Minimum Inhibitory Concentrations of the antibiotics against some drug resistant strains, thus potentiating their antimicrobial activities (Sibanda and Okoh, 2007; Darwish and Aburjai, 2010). According to some studies, combinations of plant extracts and antibiotics using MICs have demonstrated synergistic effects compared to the indifferent effect of these extracts, including those with weak antibacterial activity, when they are studied by the well diffusion method (Adwan *et al*., 2010). Thus, it may be necessary to test the interaction between plant extracts tested in this study and the

antibiotics by MIC study to assess any other synergistic effects between these plants and antibiotics, especially those with low antibacterial activity.

CONCLUSION

In the present study, antibacterial activity of different plant hydromethanolic extracts against tested strains was confirmed and the data showed that combination effects of these plant extracts with all tested antibiotics had antibacterial enhancement (synergism) against most pathogenic bacteria. These results suggest the possibility of use of these antibiotics in association with plant extracts to treat infections caused by bacterial strains often characterized by their multi-drug resistance profile. It is necessary to carry out a bioassay guided fractionation of studied plant extracts in order to isolate and identify the compounds responsible for synergistic activity with antibiotics. Elucidation of action mechanisms of these compounds must be followed by toxicity and *in vivo* tests to determine applicability of such compounds in combination therapy.

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