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Research Article

Synergistic antibacterial evaluation of *Coriandri aetheroleum* and linalool with standard antibiotics

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Abstract: Within this work, it was aimed to investigate the in vitro antibacterial properties of the Pharma grade coriander (*Coriandrum sativum* L.) essential oil, and its combinations. The chemical composition of the essential oil was confirmed by gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS) analyses, simultaneously. Furthermore, the potential antibacterial activity of both the essential oil, and (+)-linalool with standard compounds chloramphenicol, and ciprofloxacin were evaluated using an in vitro microdilution assay against a panel of selected pathogens, namely *Acinetobacter baumannii, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus*. Initially, the minimum inhibitory concentrations (MIC) were determined, the essential oil as well as (+)-linalool and the standard antibiotics were combined for the synergistic antibacterial activity potential, where the combination activities were expressed as fractional inhibitory concentration index values (Σ FIC). The Coriander oil was relatively more effective against *B. cereus*, *P. aeruginosa*, *E. coli*, *A. baumannii* (2500 µg/mL) compared to *S. aureus* (5000 µg/mL), respectively. (+)- Linalool was found as effective as the essential oil (2500-5000 µg/mL). Coriander oil and antibiotic combinations showed synergistic effects against *B. cereus* (∑FIC= 0.375), *E. coli* (∑FIC= 0.078) and *S. aureus* (∑FIC= 0.375). Combination with (+)-linalool, and antibiotics showed synergistic effects against *B. cereus* (∑FIC= 0.375), *E. coli* (∑FIC= 0.093), as well as against *S. aureus* (∑FIC= 0.375), respectively. To the best of our knowledge, this is the first time of the antimicrobial combination study of linalool, coriander oil, chloramphenicol, and ciprofloxacin. The initial findings of this work suggest further natural product and drug combination evaluations.

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1. INTRODUCTION

Microorganisms develop resistance to antibiotics due to the unconscious and inappropriate use of resulting in the difficult treatment protocols (Kon & Rai, 2013). Through the intense use of antibiotics, resistant microorganisms emerged such as *Acinetobacter baumannii, Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus* among other

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pathogens. Diseases caused by multidrug-resistant microorganisms can be treated by combining plant sources with appropriate concentrations of antibiotics, especially with the antimicrobial activity of essential oils (Kon & Rai, 2013). The activity of essential oils can affect both the external envelope of the cell and the cytoplasm. The hydrophobicity of the major antibacterial compositions of essential oils enables partition in the lipids of the cell membranes and mitochondria, disturbing their structures, changing their functions and rendering the permeability (Kon & Rai, 2013).

Coriandrum sativum L. of the Apiaceae is commonly known as a "Coriander" and is originally from Eastern Mediterranean regions, which is cultivated in China, India, Europe, Egypt and Morocco (Ceylan, 1997; Hornok, 1992). It grows naturally in İstanbul, Siirt, Adıyaman, Ankara, Antalya, Çanakkale and Bursa provinces in Turkey (Bakıs *et al*., 2011). This plant is mainly used as spice and flavouring in foods and for the production of its characteristic essential oil. Coriander is known as one of the oldest spice crops in the world (Asgarpanah & Kazemivash, 2012). The plant is used as an antispasmodic, antimicrobial (Kubo *et al*., 2004), antioxidant (Ramadan *et al*., 2003; Bajpai *et al*., 2005) and antidiabetic (Gallagher *et al*., 2003) activities among other biological and pharmacological activities (Hornok, 1992; Asgarpanah & Kazemivash, 2012; Kubo *et al*., 2004; Ramadan *et al*., 2003; Bajpai *et al*., 2005; Gallagher *et al*., 2003). The phytochemical investigations on *C. sativum* have revealed the presence of essential oil, fats and oils, flavonoids, isocoumarins, sterols as well as polyphenolic compounds (Hornok, 1992; Asgarpanah & Kazemivash, 2012; Kubo *et al*., 2004; Ramadan *et al*., 2003; Bajpai *et al*., 2005, Gallagher *et al*., 2003; Özek *et al*., 2010; Beyzi *et al*., 2017). Mostly, the monoterpenoid (+)-linalool (Özek *et al*., 2010) was determined as major component (>50%) in essential oil of Coriander, while *α*-pinene, camphor, and *γ*-terpinene are present among others (Asgarpanah & Kazemivash, 2012; Özek *et al*., 2010; Beyzi *et al*., 2017).

In this present study, Pharmacopoeia grade Coriander essential oil (*Coriandri aetheroleum*) acquired from commercial sources was evaluated for its *in vitro* antibacterial properties against food and human pathogenic standard bacterial strains. Not only the oil, but also the main compound linalool, and the combinations with standard antibiotics were subjected for the synergistic potential evaluation, to the best of our knowledge for the first time.

2. MATERIAL and METHODS

2.1. Materials

Pharmacopoeia grade essential oil of Coriander (CO) from Aromapharm Company, Germany, the standard antibiotics chloramphenicol and ciprofloxacin, and (+)-linalool from commercial sources like Sigma-Aldrich (St. Louis, USA) were evaluated for its antibacterial properties, which were in pharmaceutical grade or highest possible purity.

Microorganisms strains (*Acinetobacter baumannii* ATCC 19606, *Bacillus cereus* NRRL B-3711, *Escherichia coli* ATCC 8739, *Pseudomonas aeruginosa* ATCC B888, *Staphylococcus aureus* ATCC BAA 1026) used for the evaluation of antibacterial and synergistic activity were obtained from the American Type Culture Collection (ATCC) and Agricultural Research Service Culture Collection (NRRL) in lyophilized form.

2.2. Gas Chromatography (GC) and Gas Chromatography - Mass Spectrometry (GC-MS) analysis

GC and GC-MS conditions were described previously (Demirci *et al*., 2008). Identification of the volatile components were carried out by comparison of their relative retention times with those of authentic samples or by comparison of their relative retention index (RRI) to series of *n*-alkanes. Computer matching against commercial (Wiley GC-MS Library, MassFinder 4.0 Library), (McLafferty & Stauffer, 1989; Koenig *et al*., 2004), and in-house "Başer Library of

Essential Oil Constituents" built up by genuine compounds and components of known oils, as well as MS literature data (Joulain & König, 1998) was used for the identification as also previously reported (Demirci *et al*., 2008).

2.3. Antibacterial Activity

The antibacterial activity of both the essential oil (CO) and the main compound, (+)-linalool (L) (20-0.019 mg/mL) was evaluated by broth microdilution assay according to a modified Clinical and Laboratory Standards Institute (CLSI) method as previously described (CLSI, 2006; Demirci *et al*., 2015). The standard antibiotics chloramphenicol and ciprofloxacin (128-0.25 µg/mL) were used as standard controls. Microbial growth was indicated by change in color from blue to pink with Resazurin. Solvent and microbial controls were also added to the assay plate. Antibacterial assays were repeated at least three times for all the test samples and arithmetic means were reported.

2.4. Synergistic Antibacterial Activity

Interaction of the test samples was studied using the checkerboard microdilution assay in 96-well plates (Van Vuuren *et al*., 2009; Stanojevic *et al*., 2010). Checkerboard method was performed on a 96-well plate using an 8-by-8 well platform. Eight serial dilutions, two-fold dilutions of Coriander essential oil and its main constituent, (+)-linalool (20-0.019 mg/mL) and antibiotics (128-0.25 µg/mL) were prepared. 25 µL aliquots of sample was added to the wells in a vertical orientation, and 25 µL aliquots of each antibiotics dilution were added in a horizontal orientation so that the plate contained various concentration combinations of the two compounds. Positive growth controls (to assess the presence of turbidity) were performed in wells not containing antimicrobial samples. Following this, each well was inoculated with a 50 µL ($5x10^3$ CFU/well) microorganism suspension (turbidometrically standardized), and was further incubated at 35°C for 24 hours. After incubation 20 µL of resazurin was added to all wells and left at 35°C for 2 h, microbial growth was indicated by change in colour from blue to pink. The broth microdilution checkerboard method was performed by using the fractional inhibitory concentration index (∑FIC), which is defined as the sum of the MIC of each sample, when used in combination divided by the MIC of the sample when used alone. Calculations were performed by following equations:

$$\sum FIC = FIC\ X + FIC\ Y$$

FIC X = (MIC value of combined sample and antibiotic)/(MIC value of antibiotic alone)

FIC Y = (MIC value of combined sample and antibiotic)/(MIC value of sample alone)

Consequently, the activity was defined as follows:

$\sum FIC \leq 0.5$ = synergism;

$\sum FIC\ 0.5 \leq 1$ = additive effect;

$\sum FIC > 1\text{-}4$ = indifferent effect; and as

$\sum FIC \geq 4$ = antagonism for more detailed information check references (Van Vuuren *et al*., 2009; Stanojevic *et al*., 2010) and references herein.

3. RESULTS

3.1. Gas Chromatography (GC) and Gas Chromatography - Mass Spectrometry (GC-MS) Analysis

The essential oil was analyzed to confirm its quality by GC and GC-MS, simultaneously, where the monoterpenes linalool (75 %), α-pinene (5 %), camphor (4.5 %), and γ-terpinene (3.5%) were characterized as the main constituents, complying with the quality of the supplier and Pharmacopoeia Monograph (2014). Other constituents are given in Table 1.

Table 1. Essential oil constituents of the Coriander oil.

No	RRI[a]	Compound	(%)[b]	IM[c]
1	1032	α- Pinene	5.0	tR, MS
2	1076	Camphene	0.8	tR, MS
3	1118	β-Pinene	0.4	tR, MS
4	1174	Myrcene	0.5	tR, MS
5	1203	Limonene	2.1	tR, MS
6	1255	γ-Terpinene	3.5	tR, MS
7	1280	*p*-Cymene	2.1	tR, MS
8	1290	Terpinolene	0.4	tR, MS
9	1450	*trans*-Linalool oxide	0.1	MS
10	1478	*cis*-Linalool oxide	0.1	MS
11	1532	Camphor	4.5	tR, MS
12	1553	Linalool	75.0	tR, MS
13	1706	α-Terpineol	0.3	tR, MS
14	1765	Geranyl acetate	3.5	tR, MS
15	1857	Geraniol	1.5	tR, MS
		Total	99.8	

[a]RRI: Relative retention indices calculated against *n*-alkanes; [b]%: calculated from FID data; [c]IM: Identification Method; tR, identification based on the retention times (tR) of genuine standard compounds on the HP Innowax column; MS, tentatively identified on the basis of computer matching of the mass spectra with those of the Wiley and MassFinder libraries and comparison with literature data.

3.2. Antibacterial Activity

The antibacterial properties of essential oils and their constituents play an important role in their utilization. Therefore, in the frame of this work, the antibacterial potential of the oil and its constituents were subjected to various in vitro evaluations. In the present study, the MIC values of Coriander essential oil and (+)-linalool were found as 2500 µg/mL against *B. cereus*, *P. aeruginosa*, *E. coli*, *A. baumannii* and 5000 µg/mL against the pathogen *S. aureus*. For comparison the MIC values of standard antibiotics ciprofloxacin and chloramphenicol were given in Table 2.

Table 2. Antibacterial evaluation of Coriander essential oil (CO) and its main constituent (L) (MIC; µg/mL).

Test microorganisms	CO	L	CRP	CHL
A. baumannii	2500	2500	0.25	32
B. cereus	2500	2500	0.25	4
E. coli	2500	2500	>0.125	2
P. aeruginosa	2500	2500	>0.125	16
S. aureus	5000	5000	8	64

3.3. Synergistic Antibacterial Activity

As a result of our present checkerboard experiment, Coriander essential oil showed synergistic effect with ciprofloxacin against *B. cereus* and *E. coli*, where the resulting FIC values are listed in Table 3. Coriander essential oil and chloramphenicol combination showed synergistic effects against *S. aureus* and additive effect against *A. baumannii*. However, Coriander essential oil and chloramphenicol combinations resulted in indifferent effect against *B. cereus* and *E. coli* where the FIC values are given in Table 4. Additionally, the main compound linalool showed synergistic effects with ciprofloxacin combination against *B. cereus* and *E. coli* and with chloramphenicol against *S. aureus* as seen in Tables 5-6, respectively. However, linalool and standard antibiotics combinations resulted in indifferent effect against the tested bacteria.

Table 3. Coriander oil (CO) combinations (comb) with ciprofloxacin (CPR) (µg/mL).

Test microorganisms	CO (Alone)	CO (Comb)	CRP (Alone)	CRP (Comb)	∑FIC	Results
A. baumannii	2500	78.125	0.25	0.25	1.031	Indifferent
B. cereus	2500	312.5	0.25	0.0625	**0.375**	**Synergistic**
E. coli	2500	39.062	0.125	0.0078	**0.078**	**Synergistic**
S. aureus	5000	5000	8	4	1.5	Indifferent

Table 4. Coriander oil (CO) combination (comb) with chloramphenicol (CHL) (µg/mL).

Test microorganisms	CO (Alone)	CO (Comb)	CHL (Alone)	CHL (Comb)	∑FIC	Results
A. baumannii	2500	1250	32	16	**1.0**	**Additive**
B. cereus	2500	78.125	4	4	1.031	Indifferent
E. coli	2500	78.125	2	4	2.031	Indifferent
S. aureus	5000	1250	64	8	**0.375**	**Synergistic**

Table 5. (+)-Linalool (L) combination with ciprofloxacin (CPR) (µg/mL).

Test microorganisms	L (Alone)	L (Comb)	CRP (Alone)	CRP (Comb)	∑FIC	Results
A. baumannii	2500	78.125	0.25	0.25	1.031	Indifferent
B. cereus	2500	625	0.25	0.031	**0.375**	**Synergistic**
E. coli	2500	78.125	0.125	0.0078	**0.093**	**Synergistic**
S. aureus	5000	78.125	8	8	1.015	Indifferent

Table 6. (+)-Linalool (L) combination with chloramphenicol (CHL) (µg/mL).

Test microorganisms	L (Alone)	L (Comb)	CHL (Alone)	CHL (Comb)	∑FIC	Results
A. baumannii	2500	2500	32	16	1.5	Indifferent
B. cereus	2500	78.125	4	8	2.031	Indifferent
E. coli	2500	78.125	2	2	1.031	Indifferent
S. aureus	5000	1250	64	8	**0.375**	**Synergistic**

4. DISCUSSION and CONCLUSION

The linalool enantiomers of various plants including Coriander essential oil were previously reported from our group (Özek *et al*., 2010). According to a previous work of Ebrahimi *et al*. (2010) linalool (40.9−79.9%), neryl acetate (2.3−14.2%), γ-terpinene (0.1−13.6%) and α-pinene (1.2−7.1%), were reported as the main constituents of Coriander essential oil obtained from different areas in Iran. In other study, linalool (69.8%), α-pinene (5.4%), γ-terpinene (5.3%) and camphor (5.2%) were found as main constituents for Coriander essential oil (Delaquis *et al*., 2002). Recent works of the chemical compositions of Coriander essential oil by Soares *et al*. (2012) and Scazzocchio *et al*. (2015) reported linalool concentrations of 54.6% and 48.4%, respectively.

In part of our previous work, the antibacterial activities of (-)- and (+)-linalool enantiomers showed no significant effects except against the methicillin-resistant *S. aureus* (200 µg/mL) pathogen (Özek *et al*., 2010). In contrary, in a recent study, linalool was evaluated against five different *A. baumannii* strains where MIC values were 2-8 µL/mL (eq. to 1.74 - 6.94 mg/mL) (Alves *et al*., 2016). Also, Delaquis *et al.* (2002) tested in an earlier antibacterial combination work, high concentrations of linalool fractions (65.1-97.7%), which was effective (0.04-0.47%, v/v) against the tested 5 microbial strains, where *S. aureus* (0.08-0.4%, v/v) was also present. Silva *et al*. (2011) also reported the inhibition results of Coriander essential oil against *A. baumannii* 2/10 with a value of MIC=0.08 mg/mL; for *B. cereus* ATCC 11778, MIC=0.08 mg/mL; for *E. coli* ATCC 25922, MIC=0.17 mg/mL; for *P. aeruginosa* ATCC 27853, MIC=1.42 mg/mL; and for *S. aureus* ATCC 25923, MIC=0.17 mg/mL, respectively. Additionally, the essential oil mode of action was reported through the membrane. In another study by Bazargani and Rohloff (2015), the Coriander essential oil was reported as inhibitory against *S. aureus* CCUG 4151 (MIC=0.68 mg/mL) and against *E. coli* CCUG 17620 (MIC=1.31 mg/mL). Furthermore, Coriander essential oil showed better antibacterial activity compared with chloramphenicol and ciprofloxacin using by disc diffusion method. The antibacterial activity results showed that Coriander essential oil was effective against *S. aureus* with a diameter of 19 mm inhibition, where it can also be used to control *P. aeruginosa* and *E. coli*, however with a relative less inhibition rate in an agar-based environment (Singh *et al*., 2002).

Pathogens such as Gram-positive and Gram-negative (*A. baumannii, S. aureus, B. cereus, E. coli, P. aeruginosa* etc.) are commonly found in water, soil, animals and human. In particular, food borne and spoilage microorganisms are difficult to handle in the treatment of multiple drug resistance. When standard antibiotics and essential oils are used in combination, synergistic activity can increase effectiveness (Van Vuuren *et al*., 2009; Stanojevic *et al*., 2010; Alves *et al*., 2016; Duarte *et al*., 2012; Toroğlu, 2011; Mazumder, 2014).

Previous published work on the synergistic activity by Checkerboard of Coriander essential oil and antibiotic combinations resulted in a synergistic effect with chloramphenicol, ciprofloxacin, tetracycline and gentamicin against *A. baumanii* LMG 1025 and LMG 1041 strains (Duarte *et al*., 2012). An additive effect was also reported for Coriander essential oil combined with gentamicin against the tested bacteria, except for *A. baumanii* 93641 with FICI value of 0.25 (Scazzocchio *et al*., 2015). The study by Toroglu *et al*. (2011) where Coriander essential oil was combined with Ceftriaxone resulted in an increase of antibacterial activity against *S. aureus*. Additionally, the combination of Coriander essential oil with gentamicin, cephalothin and ceftriaxone resulted in the decrease of the antimicrobial activity against *S. aureus* Cowan 1 and *E. coli* DM strains.

Mazumder *et al*. (2014) observed differences in survival rates of essential oils and bacteria. *E. coli, S. aureus* and *P. aeruginosa* antibiotics were found to be more susceptible to growth inhibition of antibiotics when Coriander essential oil was added compared to the inhibition

zones on nutrient agar plates. Ciprofloxacin and streptomycin were reduced in the combinations with Coriander essential oil further confirming synergistic activity.

As an overall result, it was observed that generally the inhibitory concentrations against a wide spectrum of pathogens were decreased with oil and antibiotic combinations to contribute also to lower the microbial resistance as well as overall toxicity. The previously reported antimicrobial study (Silva *et al*., 2011) also confirmed the mode of action of Coriander essential oil against the pathogens.

This study was performed to investigate the antimicrobial activities of Coriander essential oil and main constituent linalool against human and food pathogens. To the best of our knowledge the combination of the essential oil and the major components (+)-linalool with selected common food and human pathogens were performed in this present study. Moreover, essential oil and linalool had been shown synergistic antibacterial activities combined with standard antibiotics chloramphenicol and ciprofloxacin on particular standard pathogenic bacterial strains. Our results were also in accordance with current literature results. It can be concluded that compared with information in the literature, our Coriander and linalool inibitory results were in agreement.

These present results showed that the particular combinations could be an alternative treatment for multidrug resistance in various microbial infections in particular originating from food sources, which has to be confirmed by in-depth studies.

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Declaration of Conflicting Interests and Ethics

The authors declare no conflict of interest. This research study complies with research and publishing ethics. The scientific and legal responsibility for manuscripts published in IJSM belongs to the authors.

Authorship Contribution Statement

Gözde Öztürk: Investigation, Methodology, Formal Analysis and Writing original draft. **Gamze Göger:** Investigation, Methodology, Formal Analysis and Writing original draft. **Fatih Demirci:** Supervision and Writing original draft. **Betül Demirci:** Supervision and Critical reading.

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