

ANTIBACTERIAL PROFILE OF PEUCEDANUM LONGIFOLIUM ESSENTIAL OIL

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In the present study, the chemical composition and antibacterial activity of *Peucedanum longifolium* Waldst. & Kit. (Apiaceae) essential oil were examined, as well as the association between it and standard antibiotics. Gas chromatography and gas chromatography/mass spectrometry were used to analyze the chemical composition of the oil. The antibacterial activity of the oil was investigated by the broth microdilution method against thirteen bacterial strains. The interactions of the essential oil with three conventional antibiotics: tetracycline, streptomycin and chloramphenicol toward five selected bacterial strains were evaluated using the microdilution checkerboard assay. Monoterpene hydrocarbons (61.60%), with myrcene (15.88%) as the dominant constituent, were the most abundant compound class of the essential oil of *P. longifolium* from Serbia. The researched essential oil exhibited slight antibacterial activity against the tested bacterial strains *in vitro*. On the contrary, essential oil of *P. longifolium* possesses significant synergistic potential in combination with streptomycin and chloramphenicol (FIC indices in the range 0.21–0.87). Their combinations reduced the minimum effective dose of the antibiotic and, consequently, minimized its adverse side effects. In addition, investigated interactions are especially successful against Gram-negative bacteria, the pharmacological treatment of which is very difficult nowadays. These results indicate a method to enhance the efficacy of antibacterial drugs, especially against resistant bacterial strains. *Acta Medica Medianae* 2015; 54(1): 20-26.

Key words: *Peucedanum longifolium*, essential oil, antibiotics, checkerboard assay, synergistic interactions

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Introduction

Bacterial resistance to antimicrobial drugs is a major obstacle to the treatment of infectious diseases (1). Thus, a search for new and more sustainable antibiotics is a necessity. Many studies have shown significant antibacterial activity of essential oils against a wide range of resistant microbial strains (2,3). To enhance the efficacy of antibacterial drugs and to reduce the required concentration, their combined use with essential oils is one of the promising strategies (4,5).

The genus *Peucedanum* belongs to the Apiaceae family and consists of 120 economically important species that are used as foods and pharmaceuticals (6). *Peucedanum longifolium* Waldst. & Kit. is one of 14 species of this genus

growing wild in Serbia (7). The search of the available literature revealed no data on the antibacterial activity of *P. longifolium* essential oil, especially in the combination essential oil-conventional antibiotic.

Aim

Given the importance of *Peucedanum* species, the aim of the present study was to examine the chemical composition and antibacterial activity of *P. longifolium* essential oil, as well as its combination with standard antibiotics: tetracycline, streptomycin and chloramphenicol.

Material and Methods

Plant material and chemicals

The aerial parts of *Peucedanum longifolium* Waldst. & Kit. (Apiaceae) were collected in July 2011 from natural populations at the Rtanj mountain, Serbia. A voucher specimen, with the

accession number 16537 is deposited at the Herbarium of the Department of Botany, Faculty of Biology, University of Belgrade-Herbarium Code BEOU. All chemicals, reagents and standards were of analytical reagent grade and were purchased from the Sigma-Aldrich Chemical Company.

Oil isolation, gas chromatography, gas chromatography/mass spectrometry and identification of compounds.

Oil isolation, GC, GC-MS analyses and identification of oil compounds were performed as previously described (2).

Antibacterial testing

The activity of the essential oil samples was tested towards thirteen model bacteria. Gram-negative bacteria were represented by *Escherichia coli* ATCC 25922, *Salmonella enteritidis* ATCC 13076, *Klebsiella pneumoniae* ATCC 10031, *Klebsiella pneumoniae* ATCC 700603, *Proteus mirabilis* ATCC 12453, *Pseudomonas aeruginosa* ATCC 9027, *Pseudomonas aeruginosa* ATCC 27853 and *Enterobacter aerogenes* ATCC 13048, while the researched Gram-positive strains were *Enterococcus faecalis* ATCC 19433, *Bacillus cereus* ATCC 11778, *Staphylococcus aureus* ATCC 25923, *Staphylococcus aureus* ATCC 29213 and *Listeria monocytogenes* ATCC 15313.

The inocula of the bacterial strains were prepared from overnight broth cultures and the suspensions were adjusted to 0.5 McFarland standard turbidity (corresponding to 108 CFU/mL) depending on genera-consensus standard by the Clinical and Laboratory Standards Institute (8).

Micro-well Dilution Assay and Microdilution Checkerboard Assay

Micro-well dilution assay and microdilution checkerboard assay were used to determine the minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and to assess antimicrobial combinations in vitro, as previously described (2).

Results

Chemical composition of the essential oil

The yield of *P. longifolium* essential oil was 0.31% (w/w). Based on GC and GC-MS analysis of *P. longifolium* oil, 59 components were identified that represented 95.40% of the total detected constituents (Table 1). The monoterpene hydrocarbons were the most abundant compound class in the oil (61.60%), and they were dominated by myrcene (15.88%), α -phellandrene (11.28%) and limonene (8.23%).

Antibacterial activity

The essential oils were tested for their antibacterial activity by the broth microdilution method to determine the MIC and MBC values

against thirteen model bacteria (Table 2). The results from the antibacterial assay showed that *P. longifolium* essential oil possessed slight antimicrobial activities, with MIC and MBC values in the range from 2427.2 to 38835.2 μ g/ml. Gram-positive bacteria were generally found to be more sensitive than gram-negative ones. The reference antibiotics were active in the following ranges of concentration: tetracycline, 0.5 to 1024.0 μ g/ml; streptomycin, 0.5 to 256.0 μ g/ml and chloramphenicol, 1.0 to 2048.0 μ g/ml.

Interaction between the essential oil and antibiotics

The results of the possible interactions between the essential oil and the antibiotics are given in Table 3. From 135 tested combinations between *P. longifolium* oil and the three antibiotics, 50 (37.04%) showed synergism, while 29 (21.48%) had an additive and 56 (41.48%) had an antagonistic effect. The best antibacterial activities were obtained with the combination of *P. longifolium* oil and chloramphenicol. For this combination, a synergistic effect of 66.67% was recorded (FIC indices in the range 0.21–0.87). The highest percentage of the additive effect (26.67%) was registered again in the oil/chloramphenicol combination, while the highest percentage of the antagonistic effect (77.78%) was noted for the oil/tetracycline association. The maximum effect combination of essential oil and antibiotics was expressed toward *K. pneumoniae* ATCC 700603. The results of the checkerboard assay showed a synergistic effect of 51.85%, an additive effect of 22.22% and an antagonistic effect of 25.93% for this bacterial strain.

Discussion

The composition of essential oil isolated from the aerial parts of *P. longifolium* was found similar in comparison to the composition of the essential oil of *P. longifolium* from Orjen, Montenegro. Both essential oils accumulate monoterpene hydrocarbons, as the dominant class of compounds (9).

The antibacterial activity of *P. longifolium* essential oil displayed significant variation among the different bacteria species but remained much lower than the activities of the standard antibiotics. In research of the antibacterial activity of *Peucedanum membranacea* Boiss. against four bacteria, inhibitory values in the range 32–250 μ g/mL were found (6).

The interaction of essential oils with antibiotics is one of the novel ways to overcome bacterial resistance. The presented results of total effects of essential oil/antibiotic combinations fully justified the purpose of the study and indicated an encouraging fact, i.e., an essential oil with low antibacterial activity may exhibit synergistic and additive effects in association with conventional antibiotics. The combination of *P. longifolium* oil

Table 1. Composition of the essential oil of *P. longifolium*

Component	RT ^a (min)	AIL ^b	AIE ^c	<i>P. longifolium</i> (%)
Monoterpene hydrocarbons				61.60
α -Thujene	8.169	924.0	925.2	1.93
α -Pinene	8.409	932.0	932.3	1.80
Camphene	8.955	946.0	948.6	0.35
Sabinene	9.786	969.0	973.2	6.56
β -Pinene	9.933	974.0	977.6	2.11
Myrcene	10.461	988.0	993.2	15.88
α -Phellandrene	11.014	1002.0	1008.9	11.28
3-Carene	11.050	1008.0	1009.9	0.43
α -Terpinene	11.307	1014.0	1017.0	0.24
<i>p</i> -Cymene	11.637	1020.0	1026.1	5.92
Limonene	11.837	1024.0	1031.6	8.23
β -Phellandrene	11.885	1025.0	1032.9	3.44
β - <i>cis</i> -Ocimene	11.996	1032.0	1036.0	0.72
β - <i>trans</i> -Ocimene	12.385	1044.0	1046.7	1.74
γ -Terpinene	12.794	1054.0	1058.0	0.66
Terpinolene	13.776	1086.0	1085.0	0.22
Allocimene	15.318	1128.0	1127.7	0.09
Oxygenated monoterpenes				14.37
<i>cis</i> -Sabinene hydrate	13.361	1065.0	1073.6	7.27
<i>trans</i> -Linalool oxide	13.901	1084.0	1088.4	3.36
Perillene	14.254	1102.0	1098.2	0.25
Linalool	14.321	1095.0	1100.0	0.56
β -Thujone	14.963	1112.0	1117.8	0.06
<i>trans</i> -Pinocarveol	15.799	1135.0	1141.0	0.12
α -Phellandren-8-ol	16.918	1166.0	1171.9	0.06
Isomenthol	17.175	1179.0	1179.0	0.04
4-Terpineol	17.252	1174.0	1181.2	0.85
Myrtenol	17.636	1194.0	1191.8	0.04
<i>trans</i> -Dihydro carvone	18.072	1200.0	1204.0	1.16
<i>trans</i> -Piperitol	18.237	1207.0	1208.8	0.10
<i>trans</i> -Carveol	18.581	1215.0	1218.7	0.09
Neral	19.246	1235.0	1237.8	0.02
Cuminal	19.413	1238.0	1242.7	0.07
Carvone	19.453	1239.0	1243.9	0.06
Geranial	20.268	1264.0	1267.3	0.02
Perilla aldehyde	20.559	1269.0	1275.8	0.18
Bornyl acetate	20.859	1287.0	1284.4	0.06
Sesquiterpene hydrocarbons				15.51
α -Copaene	23.905	1374.0	1375.5	0.13
β -Bourbonene	24.171	1387.0	1383.6	0.09
β -Elemene	24.373	1389.0	1389.7	1.77
β -Caryophyllene	25.345	1417.0	1420.0	1.30
γ -Elemene	25.629	1434.0	1429.1	0.55
β - <i>trans</i> -Farnesene	26.374	1454.0	1452.8	0.34
α -Humulene	26.497	1452.0	1456.7	2.64
Alloaromadendrene	26.602	1458.0	1460.1	0.07
γ -Muurolole	27.083	1478.0	1475.4	0.34
Germacrene D	27.304	1484.0	1482.4	3.59
β -Selinene	27.552	1489.0	1490.3	2.51
α -Selinene	27.740	1498.0	1496.4	1.43
γ -Cadinene	28.226	1513.0	1512.4	0.04
δ -Cadinene	28.374	1522.0	1517.5	0.31
Germacrene B	29.606	1559.0	1559.0	0.40
Oxygenated sesquiterpenes				3.55
Spathulenol	30.177	1577.0	1578.2	1.89
Caryophyllene oxide	30.318	1582.0	1583.0	1.35
α -Cadinol	32.385	1652.0	1655.3	0.31
Phenolic compounds				0.32
Thymol	21.049	1289.0	1289.8	0.07
Carvacrol	21.329	1298.0	1297.9	0.25
Others				0.05
Hexanal	4.683	801.0	801.4	0.02
<i>trans</i> -2-Hexenal	5.988	846.0	850.2	0.01
<i>n</i> -Tricosane	48.054	2300.0	2300.1	0.02
Total				95.40

^{a)} RT=Retention time; ^{b)} AIL=Arithmetic (retention) index – literature data;

^{c)} AIE=Arithmetic (retention) index experimentally determined on HP-5MS column.

Table 2. Antibacterial activity of *P. longifolium* essential oil and reference antibiotics ($\mu\text{g/mL}$)

No.	Bacterial species	<i>P. longifolium</i>		Tetracycline		Streptomycin		Chloramphenicol	
		MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
1	Escherichia coli ATCC 25922	9708.8	19417.6	128.0	256.0	8.0	8.0	128	512
2	Salmonella enteritidis ATCC 13076	4854.4	9708.8	1.0	8.0	4.0	4.0	4.0	8.0
3	Klebsiella pneumoniae ATCC 10031	9708.8	9708.8	1.0	1.0	16.0	16.0	2.0	2.0
4	Klebsiella pneumoniae ATCC 700603	19417.6	38835.2	128.0	256.0	64.0	64.0	512.0	1024.0
5	Proteus mirabilis ATCC 12453	9708.8	19417.6	1024.0	1024.0	128.0	256.0	4.0	64.0
6	Pseudomonas aeruginosa ATCC 9027	9708.8	19417.6	4.0	32.0	8.0	8.0	4.0	16.0
7	Pseudomonas aeruginosa ATCC 27853	19417.6	38835.2	128.0	256.0	16.0	16.0	1024.0	2048.0
8	Enterobacter aerogenes ATCC 13048	9708.8	19417.6	0.5	8.0	0.5	0.5	1.0	1.0
9	Enterococcus faecalis ATCC 19433	2427.2	2427.2	4.0	4.0	4.0	4.0	2.0	4.0
10	Bacillus cereus ATCC 11778	4854.4	4854.4	0.5	0.5	0.5	0.5	1.0	4.0
11	Staphylococcus aureus ATCC 25923	9708.8	9708.8	1.0	1.0	0.5	0.5	1.0	8.0
12	Staphylococcus aureus ATCC 29213	4854.4	4854.4	128.0	256.0	4.0	32.0	8.0	32.0
13	Listeria monocytogenes ATCC 15313	4854.4	9708.8	1.0	2.0	1.0	1.0	8.0	8.0

Table 3. Antibacterial activity of *P. longifolium* oil-antibiotic combinations, represented by FIC and FIC_A indices of examining substances

Bacterial species		FIC _A indices of <i>P. longifolium</i> oil								
		0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90
E. coli ATCC 25922	^{1*}	0.21	0.32	0.43	0.54	0.65	0.76	0.87	0.98	1.09
	^{2*}	1.09	1.28	1.34	1.52	1.40	1.56	1.55	1.52	2.04
	^{3*}	1.20	1.40	1.60	1.80	2.00	2.20	2.40	2.24	2.23
K. pneumoniae ATCC 700603	^{1*}	0.43	0.44	0.56	0.68	0.65	0.76	0.87	0.98	1.09
	^{2*}	0.98	1.04	1.34	1.24	1.25	1.24	1.38	1.52	1.85
	^{3*}	0.32	0.44	0.56	0.54	0.80	0.76	0.87	0.98	1.09
P. mirabilis ATCC 12453	^{1*}	0.54	0.68	0.69	0.82	0.95	1.08	1.04	1.16	1.28
	^{2*}	0.76	0.80	1.08	1.24	1.55	1.08	1.21	1.16	1.85
	^{3*}	0.54	0.68	0.69	0.68	0.80	0.76	0.87	0.98	1.09
P. aeruginosa ATCC 27853	^{1*}	0.32	0.44	0.56	0.68	0.80	0.92	0.87	0.98	1.09
	^{2*}	0.76	0.92	1.08	1.24	1.40	1.40	1.38	1.52	2.04
	^{3*}	1.20	1.40	1.60	1.80	2.00	2.20	2.40	2.60	1.85
S. aureus ATCC 29213	^{1*}	1.20	0.68	0.69	0.82	0.65	0.76	0.87	0.98	1.09
	^{2*}	1.20	1.40	1.60	1.80	2.00	2.20	2.06	2.24	2.42
	^{3*}	0.98	1.04	1.08	0.96	0.65	0.76	0.87	0.98	1.09

* Examined combinations: oil-chloramphenicol (^{1*}); oil-tetracycline (^{2*}); oil-streptomycin (^{3*})

and tetracycline exhibited a predominantly antagonistic effect. A very strong antagonistic effect was registered against *S. aureus* ATCC 29213. It should be mentioned that the essential oil in these combinations had no effect on the decreasing of the MIC values of tetracycline, except for *P. mirabilis* ATCC 12453 and *P. aeruginosa* ATCC 27853 (the MIC value of tetracycline decreased up to 2-fold). The explanation of the mechanism of interactions that produce antagonistic effects has been less studied. Hypotheses, which are discussed in some studies, included the use of antibacterial compounds (or mixtures) that act on the same site of the bacteria, and chemical interactions among the antibacterial compounds (10).

The combination of *P. longifolium* oil and streptomycin against *K. pneumoniae* ATCC 700603 and *P. mirabilis* ATCC 12453 exhibited a strong synergistic effect and decreased the MIC value of streptomycin 10-fold. In contrast, the oil-streptomycin association against *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 performed a strong antagonistic effect and had no effect on the decreasing of the MIC values of streptomycin. Elucidation of the mechanism of antibacterial action based on the interaction of essential oil/antibiotic is not simple. All interactions between antibacterial compounds could change the effectiveness and relationships (synergistic, additive or antagonistic) in competition for the possible primary target. On the other hand, a synergistic multi-target effect could occur by involving proteins, enzymes, ribosomes, nucleic acids, receptors and ion channels (11).

The combination of *P. longifolium* oil and chloramphenicol against all the tested bacteria exhibited a predominantly synergistic effect and decreased the MIC value of chloramphenicol 10-fold, for all the tested bacterial strains, except for *P. mirabilis* ATCC 12453 (the MIC value of chloramphenicol decreased 3.3-fold). There are some generally accepted mechanisms of antibacterial interaction that produce synergism, including inhibition of protective enzymes, combination of membrane active agents, sequential inhibition of common biochemical pathways and the use of membranotropic agents to enhance the diffusion of other antimicrobials (12). Based on the present results, it could be hypothesized that the antibacterial activity and hence the synergistic effect of *P. longifolium* essential oil is connected with the high percentage of hydrocarbons, the most abundant compound class.

The antibacterial activity of hydrocarbons can be explained by the interactions of these compounds with the membrane and with membrane constituents of bacteria. As a result of

accumulated lipophilic molecules, the membrane loses its integrity, and an increase in permeability to protons and ions can be observed. In addition, it has been found that proteins embedded in the membrane are also affected (13). All these considerations prompted the hypothesis that the components of *P. longifolium* essential oil, with the hydrocarbons as the major compounds, favor the mechanism of action of chloramphenicol, the main effect of which is the inhibition of the bacterial enzyme peptidyl transferase, thereby preventing the growth of the polypeptide chain during protein synthesis (14). The obtained results indicate that chloramphenicol, not currently used as a therapeutic agent against gram-negative bacteria, in combination with an appropriate essential oil has significant antibacterial activity, especially against gram-negative bacteria. Moreover, its minimum effective dose is significantly reduced, and consequently possible toxic side effects are decreased. In addition, it can be assumed that in research of the antibacterial effects of essential oil-antibiotic combinations, the choice of gram-negative or gram-positive bacterial species is not decisively significant. In other words, the proper essential oil-antibiotic association will act equally stronger or weaker against all gram-positive and gram-negative bacterial strains.

Conclusion

In the present study, the chemical composition of *P. longifolium* essential oil was examined and a correlation among the anti-bacterial activities of the essential oil-antibiotic combinations was realized. It was shown that monoterpene hydrocarbons, with myrcene (15.88%) as the dominant constituent, were the most abundant compound class of the essential oil of *P. longifolium* from Serbia. The researched essential oil exhibited slight antibacterial activity against the tested bacterial strains *in vitro*. On the contrary, essential oil of *P. longifolium* possesses significant synergistic potential in combination with streptomycin and chloramphenicol (FIC indices in the range 0.21–0.87). These combinations reduced the minimum effective dose of the antibiotics and, consequently, minimized their adverse side effects. In addition, investigated interactions are especially successful against gram-negative bacteria, the pharmacological treatment of which is very difficult nowadays.

Acknowledgments

This research was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant Nos. OI 171025 and TR 31079).

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ANTIBAKTERIJSKI PROFIL ETARSKOG ULJA PEUCEDANUM LONGIFOLIUM

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U ovoj studiji ispitan je hemijski sastav i antibakterijska aktivnost etarskog ulja *Peucedanum longifolium* Waldst. & Kit. (Apiaceae). Takođe, ispitane su i kombinovane interakcije etarskog ulja i standardnih antibiotika. Gasna hromatografija i gasna hromatografija/masena spektrometrija korišćene su za analizu hemijskog sastava ulja. Antibakterijska aktivnost ulja ispitana je metodom mikrodilucije na trinaest bakterijskih sojeva. Kombinovane interakcije etarskog ulja i konvencionalnih antibiotika: tetraciklina, streptomicina i hloramfenikola ispitane su na pet bakterijskih sojeva primenom Checkerboard testa. Monoterpenski ugljovodonici (61,60%), sa mircenom (15,88%) kao dominantnom komponentom, najzastupljenija su klasa jedinjenja etarskog ulja *P. longifolium*. Ispitano etarsko ulje pokazalo je slabu antibakterijsku aktivnost prema testiranim bakterijskim sojevima u in vitro uslovima, međutim, njegova kombinovana primena sa streptomycinom i hloramfenikolom (FIC indeksi u opsegu 0,21-0,87) pokazala je izvanredan sinergistički potencijal. Kombinovana primena ulja i antibiotika smanjuje minimalnu efektivnu dozu antibiotika i minimizira negativne sporedne efekte njihovog korišćenja. Ispitane interakcije su posebno uspešne protiv Gram-negativnih bakterija, čiji je farmakološki tretman danas veoma komplikovan. Ovi rezultati ukazuju na nov način poboljšanja efikasnosti antibakterijskih lekova, posebno protiv rezistentnih bakterijskih sojeva. *Acta Medica Medianae* 2015; 54(1):20-26.

Ključne reči: *Peucedanum longifolium*, etarsko ulje, antibiotici, Checkerboard test, sinergističke interakcije