

A Design of Experiment approach for Ionic Liquid-based Extraction of Toxic Components-Minimized Essential Oil from *Myristica fragrans* Houtt. Fruits.

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[‡]Dedicated to Professor M. Curini on the occasion of his 70th birthday

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^a Percentage obtained by FID peak-area normalization. Values are presented as the mean of two extractions;

^b Components are listed in order of their elution from a DB-5MS column;

^c Identification: by comparison of the mass spectrum with those of the computer WILEY275 library (99% matching);

^dNI: not identified.

Table S1. Composition of the essential oils of *Myristica fragrans* obtained by using NaCl 0.5M.

Component^{a,b}	%
α -Thujene	0.20
α -Pinene	3.31
Sabinene	9.03
β -Pinene	5.08
Myrcene	0.72
α -Phellandrene	0.47
α -Terpinene	1.03
<i>p</i> -Cymene	0.96
Limonene	3.54
γ -Terpinene	1.94
<i>cis</i> -Sabinene hydrate	0.23
Terpinolene	0.62
Linalool	0.48
<i>p</i> -Menth-2-en-1-ol <i>cis</i>	0.36
<i>p</i> -Menth-2-en-1-ol <i>trans</i>	0.23
Terpinen-4-ol	8.25
α -Terpineol	0.95
<i>trans</i> -Piperitol	0.15
Bornyl acetate	0.13
Safrole	1.82
α -Cubebene	0.10
Eugenol	2.70
α -Copaene	0.57
Methyl eugenolo	3.27
β -Caryophyllene	0.20
Isoeugenol	0.44
Methyl isoeugenol	0.79
Myristicin	50.48
Elemicin	1.17
NI ^d	0.36
Myristic acid	
NI ^d	
Total (%)	99.56
Total identified	99.21
Monoterpene hydrocar.	27.12
Oxygenated monoterpenes	10.55
Sesquiterpene hydrocar.	0.8/8
Phenols	60.66
Acids	0

Table S2. Composition of the essential oils of *Myristica fragrans* obtained by common hydrodistillation and by using 0.5M IL 5.

Component	H ₂ O (%) ^{a,b}	IL 5 (%) ^{a,b}	RI ^{c,d}	RI Lit. ^e
α -Thujene		0.11±0.10	925	930
α -Pinene	1.09±0.06	1.18±0.08	933	939
Sabinene	2.23±0.11	1.42±0.09	975	975
β -Pinene	1.62±0.08	1.65±0.12	978	979
Myrcene		0.37±0.07	989	990
α -Phellandrene	0.10±0.12	0.40±0.10	1004	1002
α -Terpinene	0.29±0.01	3.22±0.04	1015	1017
<i>p</i> -Cymene		1.04±0.012	1023	1024
Limonene	0.97±0.08	3.11±0.07	1030	1029
γ -Terpinene	0.57±0.07	5.01±0.05	1059	1059
<i>cis</i> -Sabinene hydrate	0.30±0.02	1.77±0.08	1070	1070
Terpinolene	0.27±0.05	0.14±0.07	1084	1088
Linalool	0.47±0.10		1099	1090
<i>p</i> -Menth-2-en-1-ol <i>cis</i>	0.44±0.11		1120	1121
<i>p</i> -Menth-2-en-1-ol <i>trans</i>	0.28±0.08		1140	1140
Terpinen-4-ol	10.03±0.01	19.57±0.14	1182	1177
α -Terpineol	1.45±0.16	4.91±0.12	1190	1188
<i>trans</i> -Piperitol	0.32±0.08		1214	1207
Bornyl acetate		2.44±0.08	1285	1288
Safrole	2.90±0.11	1.66±0.09	1289	1287
α -Cubebene	0.94±0.08	0.17±0.06	1344	1348
Eugenol	2.16±0.05	0.91±0.07	1356	1359
α -Copaene	0.62±0.10	0.30±0.03	1379	1376
Methyl eugenolo	7.15±0.16	3.51±0.12	1405	1403
β -Caryophyllene	0.33±0.15	1.37±0.08	1420	1417
Isoeugenol	0.24±0.14	0.20±0.09	1459	1447
Methyl isoeugenol	1.08±0.05	0.53±0.05	1504	1491
Myristicin	57.91±0.09	40.20±0.05	1522	1517
Elemicin	2.88±0.26	1.60±0.15	1556	1555
NI ^f	1.16±0.16	0.37±0.18	1647	
Myristic acid	0.89±0.40	2.00±0.25	1774	
NI ^f	0.87±0.21	0.55±0.09	1840	
Total (%)	99.57	99.68		
Total identified	97.54	98.76		
Monoterpene hydrocarbons	7.44	19.40		
Oxygenated monoterpenes	13.00	26.92		

Sesquiterpene	1.89	1.84
hydrocarbons		
Phenols	74.32	48.61
Acids	0.89	2.00

Table S3. Composition of the essential oils of *Myristica fragrans* obtained by using IL 1.^a

Component^{b,c}	Exp. n° 8	Exp. n° 9	Exp. n° 10
α -Thujene	0.40	0.38	0.40
α -Pinene	4.17	2.55	2.08
Sabinene	10.65	8.32	7.61
β -Pinene	4.08	3.24	2.75
Myrcene	0.42	0.12	0.20
α -Phellandrene	0.13	0.29	0.20
α -Terpinene	0.15	0.12	0.10
<i>p</i> -Cymene	0.46	0.46	0.34
Limonene	0.48	0.58	0.43
γ -Terpinene	1.46	0.67	0.95
<i>cis</i> -Sabinene hydrate	0.39	0.38	0.38
Terpinolene	0.71	0.89	0.71
Linalool	0.87	0.26	0.60
<i>p</i> -Menth-2-en-1-ol <i>cis</i>	0.84	0.17	0.20
<i>p</i> -Menth-2-en-1-ol <i>trans</i>	0.13	0.11	0.14
Terpinen-4-ol	3.82	3.42	3.66
α -Terpineol	0.50	0.61	0.64
<i>trans</i> -Piperitol			
Bornyl acetate			
Safrole	2.31	2.09	2.50
α -Cubebene	0.13	0.15	0.12
Eugenol	0.80	0.62	0.63
α -Copaene	0.12	0.24	0.16
Methyl eugenolo	1.91	1.55	1.73
β -Caryophyllene	0.21	0.29	0.29
Isoeugenol	0.15	0.19	0.15
Methyl isoeugenol	0.20	0.35	0.15
Myristicin	62.80	69.29	70.50
Elemicin	0.78	1.14	0.75
NI ^d	0.14	0.16	0.15
Myristic acid	0.78	1.01	1.12
NI ^d			
Total (%)	99.98	99.65	99.64
Total identified	99.84	98.49	98.49
Monoterpene hydrocar.	23.49	18.01	16.165
Oxygenated monoterpenes	6.16	4.56	5.24
Sesquiterpene hydrocar.	0.46	0.67	0.56
Phenols	68.95	75.23	76.41
Acids	0.78	1.01	1.12

Table S4. Composition of the essential oils of *Myristica fragrans* obtained by using IL 2.^a

Component^{b,c}	Exp. n° 1	Exp. n° 5	Exp. n° 2
α -Thujene	0.30	0.39	0.28
α -Pinene	2.40	2.72	3.26
Sabinene	7.11	7.03	
β -Pinene	2.31	2.14	7.88
Myrcene	0.56	0.67	3.42
α -Phellandrene			0.67
α -Terpinene	0.98	1.21	
<i>p</i> -Cymene	0.55	0.70	0.87
Limonene	1.82	1.97	0.94
γ -Terpinene	1.31	1.40	3.31
<i>cis</i> -Sabinene hydrate			2.45
Terpinolene	0.42	0.59	
Linalool	0.40	0.55	0.37
<i>p</i> -Menth-2-en-1-ol <i>cis</i>	0.31	0.48	0.31
<i>p</i> -Menth-2-en-1-ol <i>trans</i>			0.36
Terpinen-4-ol	8.09	8.23	0.39
α -Terpineol	1.72	1.69	9.59
<i>trans</i> -Piperitol	0.19	0.25	1.21
Bornyl acetate	0.14	0.15	0.19
Safrole	3.20	3.83	3.78
α -Cubebene	0.46	0.38	0.69
Eugenol	1.56	2.41	1.60
α -Copaene	0.56	0.51	0.64
Methyl eugenolo	3.54	5.86	4.45
β -Caryophyllene	0.56	0.57	0.28
Isoeugenol	0.31	0.45	0.22
Methyl isoeugenol	1.42	1.23	1.01
Myristicin	53.12	48.82	48.24
Elemicin	0.42	1.47	1.39
NI ^d	0.10	0.21	0.10
Myristic acid	3.14	3.76	1.88
NI ^d	0.42	0.16	
Total (%)	97.42	99.81	99.76
Total identified	97.01	99.44	99.72
Monoterpene hydrocar.	17.77	18.81	23.44
Oxygenated monoterpenes	10.85	11.16	12.05
Sesquiterpene hydrocar.	1.58	1.46	1.61
Phenols	63.57	64.07	60.68
Acids	3.14	3.76	1.88

Table S5. Composition of the essential oils of *Myristica fragrans* obtained by using IL 3.^a

Component^{b,c}	Exp. n° 13	Exp. n° 14	Exp. n° 15
α -Thujene	1.07	0.98	0.82
α -Pinene	7.10	7.02	5.90
Sabinene	13.01	13.13	13.50
β -Pinene	1.80	2.86	3.22
Myrcene	1.16	0.62	0.78
α -Phellandrene	0.52	0.39	0.68
α -Terpinene	1.15	1.13	1.20
<i>p</i> -Cymene	0.90	0.69	0.92
Limonene	3.56	2.67	2.88
γ -Terpinene	1.50	1.78	1.94
<i>cis</i> -Sabinene hydrate	0.15	0.24	0.30
Terpinolene	0.71	0.47	0.39
Linalool	0.57	0.56	0.78
<i>p</i> -Menth-2-en-1-ol <i>cis</i>	0.43	0.30	0.56
<i>p</i> -Menth-2-en-1-ol <i>trans</i>	0.29	0.19	0.20
Terpinen-4-ol	9.90	7.33	7.28
α -Terpineol	1.34	0.99	1.03
<i>trans</i> -Piperitol	0.11	0.20	0.15
Bornyl acetate	0.10		0.28
Safrole	2.99	2.50	2.41
α -Cubebene	0.36	0.18	0.29
Eugenol	1.48	1.33	1.78
α -Copaene	0.32	0.26	0.33
Methyl eugenolo	4.82	3.90	3.50
β -Caryophyllene	0.14	0.12	0.20
Isoeugenol	1.05	0.94	0.77
Methyl isoeugenol	0.85	0.34	0.59
Myristicin	38.16	46.22	45.60
Elemicin	1.55	0.65	0.51
NI ^d	0.34	0.22	0.15
Myristic acid	2.21	1.43	0.29
NI ^d	0.13	0.32	
Total (%)	99.81	99.96	99.21
Total identified	99.34	99.42	99.06
Monoterpene hydrocar.	32.63	31.98	32.51
Oxygenated monoterpenes	12.78	9.57	10.28
Sesquiterpene hydrocar.	0.82	0.56	0.82
Phenols	50.90	55.88	55.16
Acids	2.21	1.43	0.29

Table S6. Composition of the essential oils of *Myristica fragrans* obtained by using IL 4.^a

Component ^{b,c}	Exp. n° 6	Exp. n° 7
α -Thujene	0.72	0.54
α -Pinene	5.18	3.76
Sabinene	7.63	2.10
β -Pinene	3.78	4.00
Myrcene	0.43	0.45
α -Phellandrene	0.19	0.59
α -Terpinene	0.20	2.38
<i>p</i> -Cymene	1.54	0.70
Limonene	2.59	2.68
γ -Terpinene	2.62	3.67
<i>cis</i> -Sabinene hydrate		
Terpinolene	0.56	0.83
Linalool	0.27	0.26
<i>p</i> -Menth-2-en-1-ol <i>cis</i>	1.25	0.12
<i>p</i> -Menth-2-en-1-ol <i>trans</i>	0.16	0.13
Terpinen-4-ol	12.27	14.39
α -Terpineol	1.20	1.15
<i>trans</i> -Piperitol	0.16	0.64
Bornyl acetate		
Safrole	1.55	2.51
α -Cubebene	0.15	0.15
Eugenol	0.90	1.36
α -Copaene	0.25	0.22
Methyl eugenolo	3.41	3.55
β -Caryophyllene		
Isoeugenol	0.42	0.34
Methyl isoeugenol	0.54	
Myristicin	47.38	46.51
Elemicin	1.47	2.11
NI ^d	0.13	0.43
Myristic acid	2.05	4.04
NI ^d	0.12	0.17
Total (%)	99.09	99.82
Total identified	98.85	99.23
Monoterpene hydrocar.	25.44	21.70
Oxygenated monoterpenes	15.31	16.74
Sesquiterpene hydrocar.	0.40	0.46
Phenols	55.65	56.38
Acids	2.05	4.04

Table S7. Composition of the essential oils of *Myristica fragrans* obtained by using IL 5.^a

Component ^{b,c}	Exp. n° 11	Exp. n° 12
α -Thujene	0.18	0.11
α -Pinene	1.35	1.18
Sabinene	2.33	1.42
β -Pinene	1.86	1.65
Myrcene	0.33	0.37
α -Phellandrene	0.30	0.40
α -Terpinene	2.03	3.22
<i>p</i> -Cymene	0.61	1.04
Limonene	2.43	3.11
γ -Terpinene	3.74	5.01
<i>cis</i> -Sabinene hydrate		1.77
Terpinolene	1.00	0.14
Linalool	0.24	
<i>p</i> -Menth-2-en-1-ol <i>cis</i>		
<i>p</i> -Menth-2-en-1-ol <i>trans</i>		
Terpinen-4-ol	19.76	19.57
α -Terpineol	2.47	4.91
<i>trans</i> -Piperitol	0.45	
Bornyl acetate	0.60	2.44
Safrole	2.70	1.66
α -Cubebene	0.19	0.17
Eugenol	1.30	0.91
α -Copaene	0.22	0.30
Methyl eugenolo	3.53	3.51
β -Caryophyllene	1.18	1.37
Isoeugenol	0.51	0.20
Methyl isoeugenol		0.53
Myristicin	44.11	40.20
Elemicin	1.85	1.60
NI ^d	0.33	0.37
Myristic acid	4.02	2.00
NI ^d		0.55
Total (%)	99.59	99.68
Total identified	99.26	98.76
Monoterpene hydrocar.	16.13	19.40
Oxygenated monoterpenes	23.52	26.92
Sesquiterpene hydrocar.	1.58	1.84
Phenols	54.01	48.61
Acids	4.02	2.00

Table S8. Composition of the essential oils of *Myristica fragrans* obtained by using IL 6.^a

Component^{b,c}	Exp. n° 3	Exp. n° 4
α -Thujene		
α -Pinene	0.74	1.26
Sabinene	0.55	0.45
β -Pinene	1.26	1.55
Myrcene	0.19	0.30
α -Phellandrene	0.39	0.54
α -Terpinene	2.06	2.71
<i>p</i> -Cymene	0.51	0.56
Limonene	2.19	2.42
γ -Terpinene	3.99	4.59
<i>cis</i> -Sabinene hydrate		
Terpinolene	1.20	1.41
Linalool		0.20
<i>p</i> -Menth-2-en-1-ol <i>cis</i>		
<i>p</i> -Menth-2-en-1-ol <i>trans</i>		
Terpinen-4-ol	23.20	19.12
α -Terpineol	4.40	4.26
<i>trans</i> -Piperitol		
Bornyl acetate	2.11	2.04
Safrole	3.25	2.56
α -Cubebene	0.17	0.13
Eugenol	0.90	1.00
α -Copaene	0.25	0.17
Methyl eugenolo	2.81	3.20
β -Caryophyllene		1.53
Isoeugenol		0.14
Methyl isoeugenol	1.13	1.24
Myristicin	45.30	42.54
Elemicin	1.35	1.47
NI ^d		0.27
Myristic acid	1.59	2.67
NI ^d		
Total (%)	99.94	98.31
Total identified	99.94	98.05
Monoterpene hydrocar.	13.07	15.78
Oxygenated monoterpenes	30.11	25.62
Sesquiterpene hydrocar.	0.42	1.83
Phenols	54.74	52.14
Acids	1.59	2.67

Table S9. *P*-values for all the coefficients

PhenylProp	Coeff. SC	Std. Err.	P	Conf. int(±)
Constant	59,1907	0,572765	8,58677e-14	1,3208
cation	DF = 2			
cat(Me)	8,10179	0,680818	2,28486e-06	1,56997
cat(Bu)	-4,6353	0,689342	0,000148943	1,58962
cat(EtOH)	-3,46649	0,703149	0,00114951	1,62146
anion	DF = 1			
ani(PO4)	-1,23141	0,601773	0,0749363	1,38769
ani(Cl)	1,23141	0,601773	0,0749363	1,38769
IL-M	0,208447	0,599789	0,737156	1,38311
cation x anion	DF = 2			
cat(Me) x ani(PO4)	-3,35341	0,693404	0,00129444	1,59899
cat(Me) x ani(Cl)	3,35341	0,693404	0,00129444	1,59899
cat(Bu) x ani(PO4)	1,47396	0,687305	0,064319	1,58492
cat(Bu) x ani(Cl)	-1,47396	0,687305	0,064319	1,58492
cat(EtOH) x ani(PO4)	1,87945	0,738598	0,0344618	1,70321
cat(EtOH) x ani(Cl)	-1,87945	0,738598	0,0344618	1,70321
cat x IL-	DF = 2			
cat(Me)*IL-	0,579732	0,665761	0,409242	1,53524
cat(Bu)*IL-	-1,17732	0,651857	0,108537	1,50318
cat(EtOH)*IL-	0,597584	0,738941	0,44207	1,704
ani*IL-	DF = 1			
ani(PO4)*IL-	-0,98695	0,584587	0,129833	1,34806
ani(Cl)*IL-	0,98695	0,584587	0,129833	1,34806
Yield	Coeff. SC	Std. Err.	P	Conf. int(±)
Constant	1,20131	0,00907023	1,18091e-14	0,0209159
cation	DF = 2			
cat(Me)	-0,100847	0,0107813	1,39443e-05	0,0248618
cat(Bu)	0,0802443	0,0109163	7,98742e-05	0,0251731
cat(EtOH)	0,020603	0,011135	0,101431	0,0256772
ani	DF = 1			
ani(PO4)	-0,0438468	0,0095296	0,00175289	0,0219753
ani(Cl)	0,0438468	0,0095296	0,00175289	0,0219753
IL-M	0,0925136	0,00949818	1,03284e-05	0,0219028

cat x ani	DF = 2			
cat(Me) x ani(PO4)	-0,0289097	0,0109807	0,0300479	0,0253214
cat(Me) x ani(Cl)	0,0289097	0,0109807	0,0300479	0,0253214
cat(Bu) x ani(PO4)	0,0182545	0,0108841	0,132031	0,0250987
cat(Bu) x ani(Cl)	-0,0182545	0,0108841	0,132031	0,0250987
cat(EtOH) x ani(PO4)	0,0106553	0,0116963	0,388923	0,0269718
cat(EtOH) x ani(Cl)	-0,0106553	0,0116963	0,388923	0,0269718
cat x IL-	DF = 2			
cat(Me) x IL-	-0,0185567	0,0105429	0,116427	0,0243119
cat(Bu) x IL-	-0,0449436	0,0103227	0,00243267	0,0238042
cat(EtOH) x IL-	0,0635002	0,0117018	0,000625904	0,0269843
ani x IL-	DF = 1			
ani(PO4) x IL-	0,0316184	0,00925745	0,00914913	0,0213477
ani(Cl) x IL-	-0,0316184	0,00925745	0,00914913	0,0213477

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