药对青蒿-藿香挥发油成分的气相色谱-质谱和化学计量学分析

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摘要: 采用气相色谱-质谱 (GC-MS) 法分离检测药对青蒿-藿香以及藿香、青蒿挥发油成分, 并利用化学计量学解析法对产生的二维色谱-质谱数据进行解析, 得到各组分的纯色谱曲线和质谱, 在质谱库中进行相似检索, 实现对组分的定性, 再用总体积积分法进行定量。实验结果表明, 青蒿-藿香药对挥发油与单味药藿香、青蒿挥发油在质与量上均有明显差异。药对青蒿-藿香及藿香、青蒿挥发油鉴定的组分分别为 70、48 和 69 个, 分别占总含量的 85.93%、93.23%和 88.85%。药对青蒿-藿香的挥发油成分主要来自青蒿, 但藿香组分的相对含量较高。药对青蒿-藿香与青蒿、藿香的共有活性组分分别为 51 和 34 个; 药对新增组分 7 个, 主要为青蒿酸 (2.99%)、对丙烯基茴香醚 (1.92%)。

关键词: 药对青蒿-藿香; 挥发油; 气相色谱-质谱; 化学计量学解析法

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Analysis of essential oil in herbal pair *Artemisia annua-Agastache rugosa* by GC-MS and chemometric resolution method

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Abstract: Gas chromatograph-mass spectrometry, chemometric resolution method (CRM) and overall volume integration method were used to analyze the essential components of herbal pair *Artemisia annua-Agastache rugosa* (AA-AR) and compare it with that of single herbs AA and AR. The results showed that the components of volatile oil of herbal pair (AA-AR) were different from that of single herb drug in quality and quantity. 70, 69, and 48 essential components in essential oil of herbal pair (AA-AR), AA and AR were determined, accounting for about 85.93%, 88.85% and 93.23% of the total volatile oil, respectively. The volatile active components of the essential oils compounds in number are almost the sum of that of two single herbs, are mainly from herb AA, and the contents of each component from herb AR were relatively high. There are 51 common active constituents shared by herbal pair AA-AR and AA, and 34 common active constituents shared by herbal pair AA-AR and AR. There are 7 new components in the essential oils of herbal pair AA-AR, the relative content of arteannuic acid (2.99%) and *p*-propenyl-anisole (1.92%) are higher than others.

Key words: herbal pair *Artemisia annua-Agastache rugosa*; essential oil; GC-MS; chemometric resolution method

药对是中药配伍的基本单位, 是复方配伍中最基本、最常用的形式[1]。两个单味药配伍, 或增强药物功效, 或减低药物毒副作用。单味药配伍后, 其化学成分有何变化及其与单味药的关系, 即药对化学[2], 是复方化学的核心, 值得深入研究。青蒿-藿香为常用抗疟药对[3]。青蒿 (*Artemisia annua* L.) 为菊科蒿属一年生草本植物,具清热解暑,除蒸截疟的功效, 挥发油为其主要有效部位之一, 具有抗菌消炎、解热止咳、平喘等药理作用[4]。藿香[*Agastache rugosa* (Fisch.

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Et Mey.) O.Ktze]为唇形科一年生或多年生草本植物，其主要成分含藿香挥发油，有抑菌防腐作用，对浅表层皮肤真菌感染也有治疗作用[5−7]。青蒿与藿香配伍临床应用可以增强清热解暑和抗疟功效[3, 8, 9]。然而，关于青蒿-藿香药对抗疟增效的内在机制以及是否与挥发油成分变化有关，目前未见报道。因此，本文利用气相色谱-质谱 (GC-MS) 法分离检测药对青蒿-藿香、单味药青蒿和藿香的挥发油成分，并采用化学计量学解析法 (chemometric resolution method, CRM) 对二维 GC-MC 数据进行处理。CRM 解析 Help 法是二维 GC-MS 数据解析的一种有效方法，利用二维矩阵数据包含的色谱/光谱信息，采用局部因子分析以分辨出各组分的纯色谱和光谱，其原理与解析方法见文献[10, 11]，已成功用于一些中药挥发油成分的分析[12, 13]。据此得到药对和各单味药的纯色谱曲线和质谱，继而凭质谱库对分辨的纯组分进行定性，再采用总体积积分法对各组分定量，最后比较了药对与单味药的挥发油成分，分析了单味药配伍后挥发油成分的变化，以进一步揭示青蒿与藿香配伍的药理基础。

材料与方法

仪器与材料 日本岛津 QP2010 型气相色谱-质谱仪。青蒿、藿香 (分别简写为 AA、AR) 购自湖南中药研究院附属医院门诊部药房，并经何桂云副主任医师鉴定。

挥发油的提取 分别对藿香、青蒿原料粉碎，过 40 目筛后各称取 200 g，按中华人民共和国药典 (2005 版)[14]挥发油提取法分别提取单味药挥发油。药对挥发油提取则是分别称取藿香、青蒿粉碎过筛原料 200 g 后混合，按照单味药挥发油提取方法提取。

色谱条件 色谱柱:DB-1 (30 m × 0.25 mm)。升温程序: 起始温度 60 ℃，维持 3 min。以 4 ℃·min^{-1} 升至 220 ℃，维持 2 min。载气 (He) 流速 1.0 mL·min^{-1}; 进口温度 280 ℃。分流比 100∶1，进样量 1 μL。

质谱条件 EI 离子源; 电子能量 70 eV，离子源温度: 200 ℃，界面温度 250 ℃。倍增器电压: 0.80 kV，扫描范围 *m/z* 35～500; 扫描速率: 5.0 s^{-1}，溶剂延迟 2.5 min。

数据分析 数据分析在计算机上进行，采用化学计量学解析法，程序用 Matlab 6.5 编写，所分辨的质谱在 NIST107 标准质谱库中检索。

结果与讨论

1 药对挥发油化学成分的定性分析

图 1 所示为药对青蒿-藿香以及藿香、青蒿的挥发油总离子流图 (TIC)，药对青蒿-藿香的成分相对复杂，新增有明显大峰。以图 1C 中的峰簇 X (保留时间为 30.07～30.297 min) 为例说明 CRM 的应用。由峰簇 X 放大图 (图 2) 可见，峰簇 X 色谱峰曲线较平滑，似乎是一个纯色谱峰。直接从色谱库中进行检索，峰簇 X 为 9-isopropyl-1-methyl-2-methylene-5-oxatricyclo[5.4.0.0 (3, 8)]undecane ($C_{15}H_{24}O$)，相似度为 81%，该峰的左、中、右部分检索结果均不相同，且

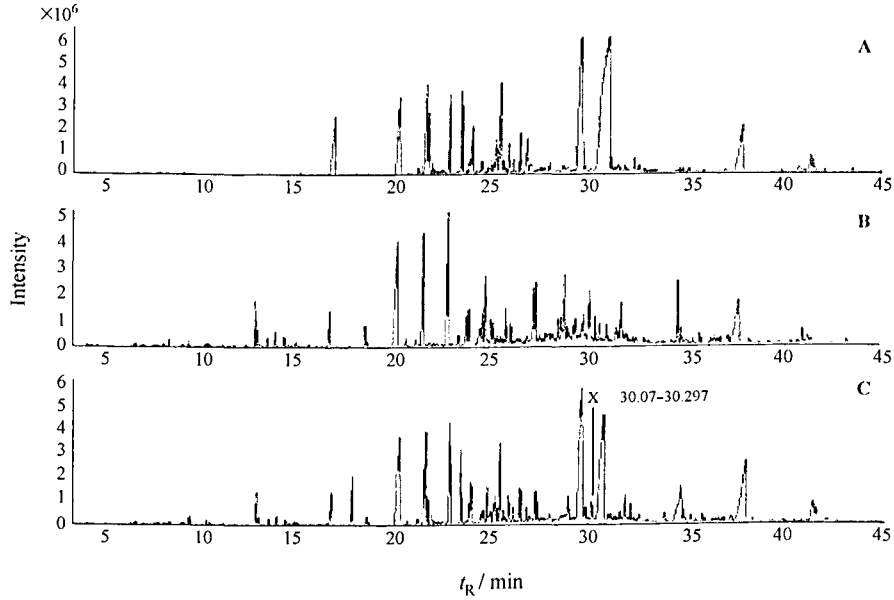

Figure 1 TICs of volatile oils of *Agastache rugosa* (A), *Artemisia annua* (B) and herbal pair *Artemisia annua-Agastache rugosa* (C)

相似度都较低，这说明峰簇 X 是重叠峰。这种重叠峰直接从色谱库中进行检索的定性结果其可靠程度和准确度都较低，也难以进行定量分析。应用 CRM 的 Help 法分析，表明峰簇 X 是两组分体系（图 3）。根据各组分的纯色谱曲线和质谱，再将它们与 NIST 库进行匹配，可检索到两组分 a、b 分别为 *cis*-Z-*α*-bisabolol epoxide ($C_{15}H_{24}O$) 和 *trans*-longipinocarveol ($C_{15}H_{24}O$)；相似度分别为 87.48%和 86.14%，相对含量分别为 0.38%和 0.57%，其相应的标准质谱与解析所得的质谱图如图 4 (左) 与图 4 (右) 所示。

按照峰簇 X 解析方法，对藿香、青蒿挥发油及其复合物的 TIC 色谱图逐步进行分辨，可得到组分的纯质谱，再用质谱库对分辨出的组分进行质谱定性检索，得到组分定性结果。为较全面的比较单味药与药对间成分变化，选取相似度大于 85%的成分进行比较分析。同时，采用正构烷烃 (C_8～C_{20}; C_{20}～C_{40}) 为内标，求得相对保留指数 (RI) 对各组分进一步定性。藿香、青蒿挥发油及药对青蒿-藿香定性鉴定的组分分别为 48、69 和 70 个，主要成分见表 1。

2 药对挥发油化学成分的定量分析

采用总体积积分法对解析后的所有色谱峰积分，得到各个组分的定量分析结果，药对青蒿-藿香及藿香、青蒿挥发油定性组分相对含量分别占总含量的 85.93%，93.23%和 88.85%，三者挥发油各主要化学成分相对含量见表 1。

3 药对与单味药挥发油成分的比较与分析

药对青蒿-藿香挥发油化学组分种类基本为 2 个单味药物的加和。在药对挥发油组分中，来自青蒿特有组分 29 个，相对含量占混合物组分的 10.19%；来自藿香特有组分 12 个，相对含量占混合物组分的 34.34%；与藿香、青蒿共有组分 22 个，相对含量占 36.23%；新检出化合物 7 个，相对含量占 5.17%。从

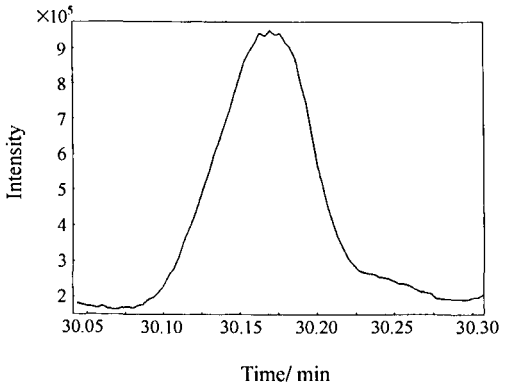

Figure 2 TIC curve for peak cluster X in Figure 1C retention time in 30.07–30.297 min

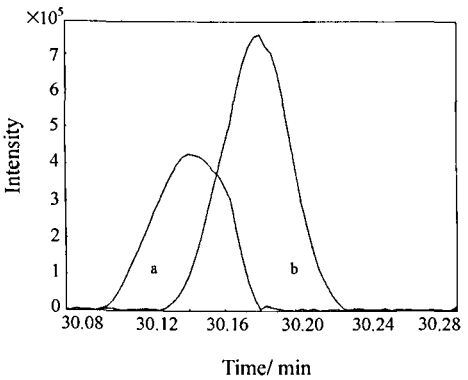

Figure 3 Resolved chromatograms for peak cluster X in Figure 1C containing two components (a and b)

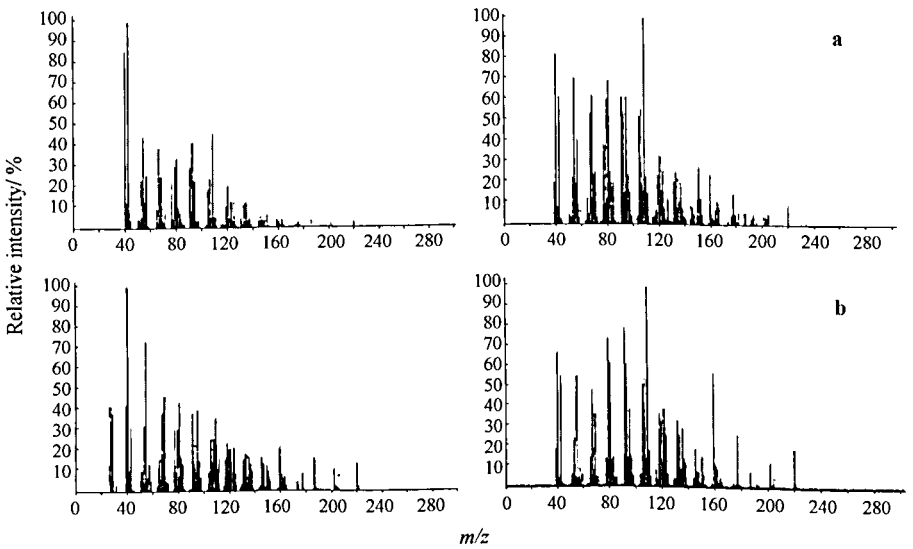

Figure 4 Resolved (right) and the standard (left) mass spectrum of the X peak clusters in Figure 1C. a: *cis*-Z-*α*-bisabolol epoxide; b: *trans*-longipinocarveol

Table 1 Main chemical components of volatile oils from *Artemisia annua* (AA), *Agastache rugosa* (AR) and herbal pair AA-AR

No.	Component/molecular formula	AA/%		AR/%		AA-AR/%		Retention index
		rc	sr	rc	sr	rc	sr	
1	α-Pinene / $C_{10}H_{16}$	0.10	95			0.07	95	886.349
2	Bicyclo[2.2.1]heptan-2-one, 1,3,3-trimethyl- / $C_{10}H_{16}O$					0.02	94	980.745
3	Eucalyptol / $C_{10}H_{18}O$	0.21	93			0.23	89	981.818
4	1,5-Heptadien-4-one, 3,3,6-trimethyl- / $C_{10}H_{16}0$	0.19	98			0.14	99	989.074
5	Bicyclo[2.2.1]heptan-2-one, 1,7,7-trimethyl-, (1*R*)- / $C_{10}H_{16}O$	2.00	97			1.02	96	1 080.064
6	Bicyclo[3.1.1]heptan-3-ol, 6,6-dimethyl-2-methylene-, [1*S*-(1α,3α,5α)]- / $C_{10}H_{16}O$	0.57	95			0.24	96	1 080.843
7	Anisole, *p*-allyl- / $C_{10}H_{12}O$					0.08	95	1 081.429
8	Bicyclo[2.2.1]heptan-3-one, 6,6-dimethyl-2-methylene- / $C_{10}H_{14}O$	0.35	89			0.15	89	1 083.981
9	Borneol / $C_{10}H_{18}O$	0.81	95			0.34	94	1 086.593
10	3-Cyclohexen-1-ol, 4-methyl-1-(1-methylethyl)- / $C_{10}H_{18}O$	0.41	89			0.13	93	1 089.504
11	1-Pentanone, 1-(2-furanyl)- / $C_9H_{12}O_2$					0.05	90	1 169.966
12	Anisole, *p*-propenyl- / $C_{10}H_{12}O$					1.92	97	1 176.909
13	Benzylidenemalonaldehyde / $C_{10}H_8O$	2.29	96	4.16	96	1.57	96	1 183.389
14	4-Hydroxy-3-methylacetophenone / $C_9H_{10}O_2$	1.23	89			0.34	89	1 189.597
15	Eugenol / $C_{10}H_{10}O_2$	12.79	96	5.90	96	6.90	96	1 280.601
16	4,7-Methanoazulene, 1,2,3,4,5,6,7,8-octahydro-1,4,9,9- tetramethyl-, [1*S*-(1α,4α,7α)]- /$C_{15}H_{24}$			2.27	95	0.82	95	1 284.767
17	Copaene /$C_{15}H_{24}$	7.47	96	4.71	95	4.14	96	1 286.657
18	Bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methylene- / $C_{15}H_{24}$	10.75	95	3.09	95	4.86	95	1 375.102
19	2-Isopropenyl-4a,8-dimethyl-1,2,3,4,4a,5,6,8a-octahydronaphthalene / $C_{15}H_{24}$			3.56	88	2.68	89	1 375.321
20	4,7,10-Cycloundecatriene, 1,1,4,8-tetramethyl-, *cis*, *cis*, *cis*- / $C_{15}H_{24}$	1.17	95			0.61	94	1 376.782
21	1,6,10-Dodecatriene, 7,11-dimethyl-3-methylene-, (*Z*)- /$C_{15}H_{24}$	1.68	92	0.45	92	2.15	90	1 377.250
22	Naphthalene, 1,2,3,5,6,7,8,8a-octahydro-1,8a-dimethyl-7-(1- methylethenyl)-, [1*R*-(1α,7β,8aα)]- / $C_{15}H_{24}$	0.95	91	0.08	90	0.14	88	1 379.294
23	Naphthalene, 1,2,3,4,4a,5,6,8a-octahydro-7-methyl-4-methylene-1-(1-methylethyl)-, (1α,4aα,8aα)- / $C_{15}H_{24}$			0.37	90	0.44	90	1 379.408
24	Patchoulene / $C_{15}H_{24}$			0.46	95	0.54	90	1 381.108
25	Eudesma-4(14),11-diene / $C_{15}H_{24}$	3.32	92	0.15	94	1.11	95	1 382.584
26	Azulene, 1,2,3,5,6,7,8,8a-octahydro-1,4-dimethyl-7-(1-methylethenyl)-, [1*S*-(1α,7α,8aβ)]- / $C_{15}H_{24}$			4.19	93	3.08	95	1 383.210
27	1*H*-Cycloprop[e]azulene, 1a,2,3,4,4a,5,6,7b-octahydro-1,1,4,7-tetramethyl-, [1a*R*-(1aα,4α,4aβ,7bα)]- / $C_{15}H_{24}$			2.56	90			1 383.607
28	Azulene, 1,2,3,4,5,6,7,8-octahydro-1,4-dimethyl-7-(1- methylethenyl)-, [1*S*-(1α,4α,7α)]- / $C_{15}H_{24}$	0.51	91	1.61	90	1.18	89	1 384.468
29	Germacrene D / $C_{15}H_{24}$	1.47	91			0.64	90	1 379.918
30	3-Allyl-6-methoxyphenyl acetate / $C_{12}H_{14}O_3$	1.21	89					1 387.895
31	Naphthalene, 1,2,3,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-, (1*S*-*cis*)- / $C_{15}H_{24}$	1.55	92	0.08	88	0.88	92	1 442.056
32	2-Butenal,2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)- / $C_{14}H_{22}O$			1.33	85	1.27	85	1 472.477
33	Thunbergol /$C_{15}H_{24}O$	2.70	85			1.22	89	1 475.281
34	Caryophyllene oxide /$C_{15}H_{24}O$	3.07	92			0.74	93	1 475.712
35	2-Naphthalenecarbonitrile /$C_{11}H_7N_4$	0.51	91	1.99	89			1 478.956
36	3-Cyclohexen-1-carboxaldehyde,3,4-dimethyl- /$C_9H_{14}O$	1.03	87					1 482.676
37	Cubenol /$C_{15}H_{26}O$	3.30	88			1.29	87	1 568.507
38	Patchouli alcohol /$C_{15}H_{26}O$			15.23	89	12.40	89	1 570.810
39	Longifolenaldehyde/$C_{15}H_{24}O$	1.23	91					1 571.640
40	1,4-Methanoazulen-7(1*H*)-one,Octahydro-4,8,9-tetramethyl-,(+)-/$C_{15}H_{24}O$	1.48	82					1 572.225
41	1-Oxaspiro[2.5]octane,5,5-dimethyl-4-(3-methyl-1,3-butadienyl)- /$C_{14}H_{22}O$	1.01	90					1 574.622
42	1, 2, 4-Trimethoxybenzene/$C_9H_{12}0_3$			29.44	86	12.34	86	1 574.853

Continued

No.	Component/molecular formula	AA/%		AR/%		AA-AR/%		Retention index
		rc	sr	rc	sr	rc	sr	
43	Longipinocarveol,*trans*-/$C_{15}H_{24}O$	2.37	87			0.57	86	1 575.913
44	*cis*-*Z*-*α*-Bisabolol epoxide/$C_{15}H_{24}O$	0.81	88			0.38	87	1 577.019
45	1-Cyclohexene-1-methanol, *α*,2,6,6-tetramethyl- / $C_{15}H_{26}0$	1.19	85					1 577.863
46	Cyclohexanemethanol, 4-ethenyl-*α*,*α*,4-trimethyl-3- (1-methylethenyl)-, [1*R*-(1*α*,3*α*,4*β*)]- / $C_{15}H_{26}O$	1.03	85					1 578.576
47	(+)-Longicamphenylone /$C_{14}H_{22}O$	2.65	88			1.35	87	1 666.507
48	Tetradecanoic acid /$C_{14}H_{20}0_2$			0.23	86	0.54	89	1 668.738
49	2-Pentadecanone, 6,10,14-trimethyl- /$C_{18}H_{36}O$	2.89	95	0.17	87	0.62	98	1 678.153
50	Arteannuic acid/ $C_{15}H_{22}O_2$					2.99	98	1 761.139
51	3,7,11,15-Tetramethyl-2-hexadecen-1-ol /$C_{20}H_{40}O$	0.56	91	0.16	91	0.37	91	1 764.880
52	4-Tetradecyne					0.07	87	1 765.536
53	Hexadecanoic acid, methyl ester					0.04	93	1 857.899
54	Tridecanoic acid /$C_{13}H_{26}O_2$	5.99	90	4.99	90	8.22	90	1 865.254
55	9,12-Octadecadienoic acid (*Z*,*Z*)- /$C_{18}H_{32}O_2$	0.69	93	1.15	93	1.75	90	2 057.740
56	9-Octadecenoic acid, (*E*)- /$C_{18}H_{34}O_2$	0.11	90	0.47	94	0.64	94	2 058.072

rc: Relative content ; sr: Similarity rate

挥发油组分含量来看，单味药材挥发油组分的含量在混合后均发生了变化。在药对挥发油中检出的藿香、青蒿组分，有 8 个组分含量大于或等于两种单味药中含量之和，其余均小于两种单味药材中组分含量之和。

由表 1 可见，药对青蒿-藿香挥发油的主要化学成分的数量大致是两个单味药的加和，含量较高的主要成分或来自藿香，如三甲氧基苯 (1, 2, 4-trimethoxybenzene)、绿叶醇 (patchouli alcohol) 等；或来自青蒿，如三烯醇 (cubenol)、黑松醇 (thunbergol) 等；或来自二者之叠加，如十三烷酸 (tridecanoic acid)、丁子香酚 (eugenol)、4,11,11-三甲基-8-亚甲基双环[7.2.0]十一碳-4-烯 (bicyclo[7.2.0]undec-4-ene, 4,11,11-trimethyl-8-methylene-) 等。这些主要成分在药对中的含量与在单味药中的不同。

实验结果还发现，药对挥发油中出现了 7 个单味药中没有的新的化学成分: 1,3,3-三甲基二环[2.2.1]庚烷-2-酮 (bicyclo[2.2.1]heptan-2-one, 1,3,3-trimethyl-); 对-烯丙基茴香醚 (anisole, *p*-allyl-); 对-丙烯基茴香醚 (anisole, *p*-propenyl-); 1-(2-呋喃)-1-戊酮 (1-pentanone, 1-(2-furanyl)-); 青蒿酸 (arteannuic acid); 4-十四 (碳) 炔 (4-tetradecyne); 十六 (烷) 酸甲酯 (hexadecanoic acid, methyl ester)。其中，青蒿酸与对丙烯基茴香醚含量较高，其余的含量都很低。研究[15, 16]表明，这些新化学成分中的青蒿酸与十六酸甲酯均具抑制白细胞增殖的抗癌药理活性；茴香醚是化学合成茴香脑的中间体，在碱性条件下加热也可异构化为具生理活性的茴香脑[17]；对于 1,3,3-三甲基二环[2.2.1]庚烷-2-酮和 1-(2-呋喃)-1-戊酮两种成分，均为具环状结构的羰基化合物，可能为 Maillard 反应中间体，因 Maillard 反应产物除类黑精外，反应过程中还会产生成百上千个有不同气味的中间体分子 (包括还原酮、醛和杂环化合物), Maillard 反应产物会表现出很强的抗氧化能力[18, 19]。因此，这些新化合物都具生理活性，是药对青蒿-藿香抗疟增效的物质基础。

结论

药对青蒿-藿香挥发油与单味药藿香、青蒿挥发油在质与量上均存在明显差异。药对青蒿-藿香及藿香、青蒿挥发油鉴定的组分分别为 70、48 和 69 个，分别占总含量的 85.93%、93.23%和 88.85%。药对与单味药青蒿共有的挥发油组分 51 个，与单味药藿香共有的挥发油组分 34 个，三者的共有组分 22 个，药对新增组分 7 个。药对青蒿-藿香挥发油组分主要来自于单味药青蒿，但化学组分种类基本为 2 个单味药物的加和，单味药挥发油组分的含量在药对中发生了变化。青蒿-藿香药对主要组分为三甲氧基苯 (12.34%)、绿叶醇 (12.40%)、十三烷酸 (8.22%)、丁香酚 (6.90%)、4,11,11-三甲基-8-亚甲基双环[7.2.0]十一碳-4-烯 (4.86%)、珐玥烯 (4.14%) 等。新增组分都具生理活性，主要为青蒿酸 (2.99%)、对丙烯基茴香醚 (1.92%)。两个单味药在煎煮过程中如何产生物理变化与化学反应，导致新的活性化合物群产生，还有待深入研究。

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