

粉防己中双苄基异喹啉类生物碱成分研究

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摘要:目的 对粉防己 (*Stephania tetrandra* S. Moore) 中的双苄基异喹啉类生物碱成分进行研究。方法 采用多种色谱、波谱技术对粉防己 95% (体积分数) 乙醇提取物中生物碱成分进行分离纯化与结构鉴定。结果 从粉防己 95% (体积分数) 乙醇提取物中分离得到 9 个双苄基异喹啉类生物碱, 分别为 3,4-二氧汉防己乙素(1)、汉防己甲素(2)、汉防己乙素(3)、氧化防己碱(4)、cycleahomine chloride(5)、千金藤素(6)、(1*R*,1'*S*)-*N*-formylisotetrandrine(7)、*N*-chloromethyltetrandrine(8)、thalrugosidine(9)。结论 化合物 1 为新化合物, 化合物 6,7 为首次从粉防己中分离得到, 化合物 9 为首次从千金藤属植物中分离得到。

关键词:粉防己; 化学成分; 结构鉴定; 双苄基异喹啉类生物碱

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粉防己 (*Stephania tetrandra* S. Moore) 为防己科千金藤属植物, 其干燥根是中药防己的主要来源, 又名石蟾蜍、白木香、汉防己等, 主产于浙江、安徽、江西等地^[1]。本品始载于《神农本草经》, 并被历版《中华人民共和国药典》收载^[2], 具有祛风止痛、利水消肿的功效。临床常用于治疗风湿痹痛、水肿脚气、小便不利、湿疹疮毒等疾病^[3]。粉防己中的化学成分以生物碱为主, 包括双苄基异喹啉型^[4]、单苄基异喹啉型、阿朴啡型、原小檗碱型等生物碱^[5], 此外还含有黄酮类^[6]和甾体类成分^[7-8]。现代药理研究表明, 粉防己具有抗肿瘤^[9-11]、抗多药耐药^[12-13]、抗炎^[14-15]、抗

高血压^[16]、神经调节^[17]、抗菌^[18-19]等多种活性。

为进一步明确粉防己中的化学成分, 本研究从粉防己 95% (体积分数) 乙醇提取物中分离得到 9 个双苄基异喹啉类生物碱, 分别鉴定为 3,4-二氧汉防己乙素(1)、汉防己甲素(2)、汉防己乙素(3)、氧化防己碱(4)、cycleahomine chloride(5)、千金藤素(6)、(1*R*,1'*S*)-*N*-formylisotetrandrine(7)、*N*-chloromethyltetrandrine(8)、thalrugosidine(9)。其中, 化合物 1 为新化合物, 化合物 6,7 为首次从粉防己中分离得到, 化合物 9 为首次从千金藤属植物中分离得到。化合物 1~9 的结构见图 1。

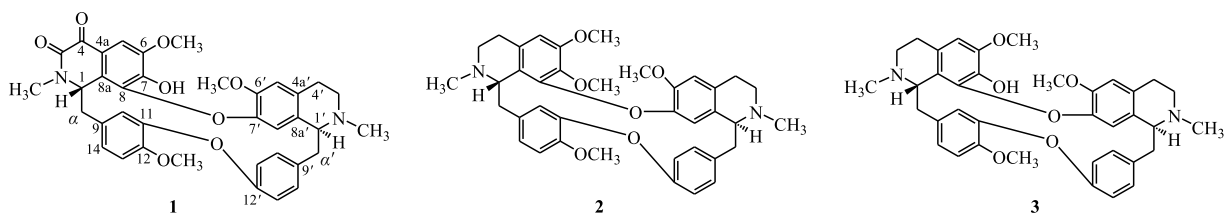
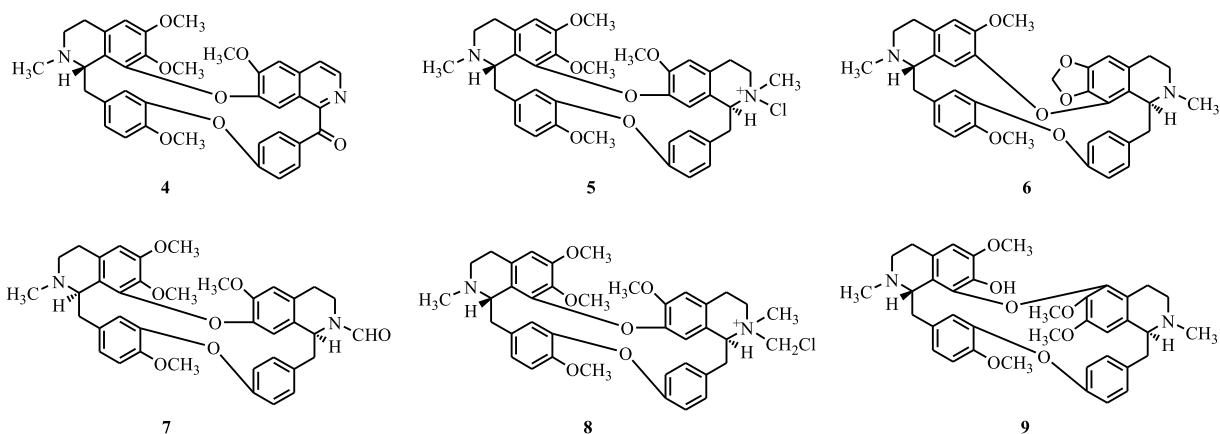


Figure 1 The structures of compounds 1-9

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Continued Figure 1

1 仪器与材料

实验所用仪器: Milli-Q 纯水净化器(美国 Millipore 公司); Waters e2695 分析型高效液相色谱仪(美国 Waters 公司); Waters 2535 制备型高效液相色谱仪(美国 Waters 公司); 岛津 LC-6AD 制备液相色谱仪(日本 shimadzu 公司); Waters Xevo G2-S UPLC-Q/TOF-MS 质谱仪(美国 Waters 公司); AUTOPOLV 旋光仪(美国 Rudolph 公司); EYELA N-1100 系列旋转蒸发器(日本东京理化 EYELA 公司); CPA225D 十万分之一电子天平(赛多利斯科学仪器有限公司); UNICO UV-6100S 分光光度计(优尼科(上海)仪器有限公司); Bruker 600 MHz 核磁共振波谱仪(瑞士 Bruker 公司)。

实验所用材料和试剂: Sephadex LH-20 色谱柱(瑞典 Pharmacia 公司); 柱色谱硅胶(200~300 目, 青岛海洋化工厂); D101 大孔吸附树脂(天津南开大学化工厂); [ODS-A-HG 色谱柱(S-50 μm)、制备型 YMC-pack-A 色谱柱(20 mm×250 mm, 5 μm)、制备型 Xbrige 色谱柱(19 mm×250 mm, 5 μm)(日本 YMC 公司)]; 制备型 COSMOSIL-PBr 色谱柱(20 mm×250 mm, 5 μm, 日本 COSMOSIL 公司); 分析级和色谱级试剂(天津康科德科技有限公司); 质谱级甲醇、乙腈(美国 Sigma 公司); 氘代试剂(青岛腾龙微波科技有限公司); 纯净水(屈臣氏公司)。

实验所用药材: 粉防己购于河北星奇有限公司, 产自湖南, 由天津中医药大学张丽娟教授鉴定为粉防己(*Stephania tetrandra* S. Moore)的干燥根。标本保存于天津中医药大学中医药研究院。

2 提取与分离

将 9.0 kg 粉防己干燥根切片, 用 10 倍量 95% (体积分数) 乙醇加热回流提取 3 次, 每次 1 h。合并后减压浓缩, 得到粗提物 4.9 kg, 提取率为 54.9%。粗提物经蒸馏水分散, 以盐酸调节 pH 值至 1.0~2.0, 用等体积乙酸乙酯萃取 3 次, 得到乙酸乙酯部分和水层部分。水层用氢氧化钠调节 pH 值至 11.0~12.0, 用等体积二氯甲烷萃取 3 次, 二氯甲烷层加入无水硫酸钠干燥, 过滤, 将滤液减压浓缩, 得到总生物碱 88.0 g。总生物碱经硅胶柱色谱(二氯甲烷-甲醇, 体积比 1:0→0:1)梯度洗脱, 得到流分 Fr1~Fr10。

Fr3(1.1 g)经 Sephadex LH-20 柱色谱(二氯甲烷-甲醇, 体积比 1:1)等度洗脱, 再经反相 ODS 柱色谱(甲醇-水, 体积比 0:100→100:0)梯度洗脱, 得到流分 Fr3-1~Fr3-6。Fr3-1 经制备液相色谱(甲醇-水, 体积比 70:30)分离纯化, 得到化合物 4(4.4 mg)和 6(3.6 mg)。Fr3-2 经制备液相色谱(乙腈-水, 体积比 65:35)分离纯化, 得到化合物 1(20.0 mg)和 5(5.4 mg)。

Fr4(35.0 g)经硅胶柱色谱(二氯甲烷-甲醇, 体积比 1:0→0:1)梯度洗脱, 得到流分 Fr4-1~Fr4-4。Fr4-1 经 Sephadex LH-20 柱色谱(二氯甲烷-甲醇, 体积比 1:1)等度洗脱, 再经反相 ODS 柱色谱(甲醇-水, 体积比 0:100→100:0)梯度洗脱, 得到流分 Fr4-1-1~Fr4-1-6。其中, Fr4-1-2 经重结晶得到化合物 2(898.0 mg), Fr4-1-4 经制备液相色谱(甲醇-水, 体积比 80:20)分离纯化, 得到化合物 9(4.1 mg)。Fr4-2 经制备液相色谱(甲醇-水, 体积比 65:35)分离纯化, 得到化合物 3

(67.0 mg)。

Fr5(21.3 g)经 Sephadex LH-20 柱色谱(二氯甲烷-甲醇,体积比 1:1)等度洗脱,再经反相 ODS 柱色谱(甲醇-水,体积比 0:100→100:0)梯度洗脱,得到流分 Fr5-1 ~ Fr5-8。Fr5-8 经制备液相色谱(甲醇-水,体积比 40:60)分离纯化,得到化合物 7(2.6 mg)。

Fr6(4.1 g)经 Sephadex LH-20 柱色谱(二氯甲烷-甲醇,体积比 1:1)等度洗脱,再经反相 ODS 柱色谱(甲醇-水,体积比 0:100→100:0)梯度洗脱,得到流分 Fr6-1 ~ Fr6-14。Fr6-14 经制备液相色谱(甲醇-水,体积比 35:65)分离纯化,得到化合物 8(8.2 mg)。

3 结构鉴定

化合物 1:黄褐色粉末。[α]_D²⁵ = +273.0° (*c* = 0.01, CHCl₃)。HR-ESI-MS *m/z*: 637.2552 [M + H]⁺ (计算值 637.2550, C₃₇H₃₆N₂O₈), 结合波谱数据确定化合物的分子式为 C₃₇H₃₆N₂O₈, 不饱和度为 21。UV (MeOH) λ_{\max} (log ϵ): 215 (8.94), 240 (3.63), 280 (3.31), 340 (1.13) nm。IR (KBr) ν_{\max} : 3427, 2919, 1654, 1508 cm⁻¹。CD

(0.14 mg·mL⁻¹, MeOH) λ_{\max} ($\Delta\epsilon$): 200 (-11.81), 244 (+18.88), 273 (-6.92), 294 (+4.01), 333 (-8.67) nm。化合物 1 的 ¹H-NMR 和 ¹³C-NMR 数据见表 1, ¹H-NMR (600 MHz, CDCl₃) 显示, δ_{H} 8.44 (1H, br s, 7-OH) 为活泼氢信号, [δ_{H} 6.85 (1H, d, *J* = 8.2 Hz, H-13), 6.73 (1H, dd, *J* = 8.2, 2.0 Hz, H-14), 6.29 (1H, d, *J* = 2.0 Hz, H-10)] 为苯环上一组 ABX 耦合氢信号; [δ_{H} 7.46 (1H, d, *J* = 8.2, 2.2 Hz, H-14'), 7.09 (1H, dd, *J* = 8.2, 2.6 Hz, H-13'), 6.92 (1H, dd, *J* = 8.2, 2.6 Hz, H-11'), 6.56 (1H, dd, *J* = 8.2, 2.2 Hz, H-10')] 提示结构中可能存在一组对位取代苯环; [δ_{H} 3.95 (3H, s, 12-OCH₃), 3.93 (3H, s, 6-OCH₃), 3.51 (3H, s, 6'-OCH₃)] 为三组甲氧基氢信号; [δ_{H} 2.90 (3H, s), 2.78 (3H, s)] 为生物碱连氮甲基氢信号。¹³C-NMR (150 MHz, CDCl₃) 给出 37 个碳信号, 关键碳信号包括两个羰基碳信号: δ_{C} 177.0 (C-4) 和 δ_{C} 159.3 (C-3); 三个甲氧基碳信号: δ_{C} 56.8 (6-OCH₃), δ_{C} 56.2 (6'-OCH₃), δ_{C} 56.0 (12-OCH₃); α -碳信号: δ_{C} 49.4; 两个连氮甲基碳信号: δ_{C} 40.9 (N'CH₃) 和 δ_{C} 37.1 (NCH₃)。

Table 1 ¹H-NMR and ¹³C-NMR spectra data of compound 1

No.	δ_{C}	δ_{H}	No.	δ_{C}	δ_{H}
1	61.3	4.81 (1H, d, <i>J</i> = 8.0 Hz)	4a'	126.6	
3	159.3		5'	112.1	6.62 (1H, s)
4	177.0		6'	149.6	
4a	130.6		7'	142.7	
5	103.5	7.29 (1H, s)	8'	119.8	6.08 (1H, s)
6	147.8		8a'	122.0	
7	137.8		α'	38.7	3.74 - 3.72 (1H, m) 2.78 - 2.76 (1H, m)
8	143.0		9'	133.4	
8a	121.8		10'	132.7	6.56 (1H, dd, <i>J</i> = 8.2, 2.2 Hz)
α	49.4	3.11 (1H, d, <i>J</i> = 13.8 Hz) 2.41 (1H, dd, <i>J</i> = 14.1, 8.9 Hz)	11'	122.7	6.92 (1H, dd, <i>J</i> = 8.2, 2.6 Hz)
9	130.4		12'	153.8	
10	114.6	6.29 (1H, d, <i>J</i> = 2.0 Hz)	13'	122.7	7.09 (1H, dd, <i>J</i> = 8.2, 2.6 Hz)
11	150.1		14'	131.0	7.46 (1H, dd, <i>J</i> = 8.2, 2.2 Hz)
12	148.1		NCH ₃	37.1	2.90 (3H, s)
13	111.8	6.85 (1H, d, <i>J</i> = 8.2 Hz)	N'CH ₃	40.9	2.79 (3H, s)
14	122.9	6.73 (1H, dd, <i>J</i> = 8.2, 2.0 Hz)	6-OCH ₃	56.8	3.93 (3H, s)
1'	63.8	4.27 (1H, d, <i>J</i> = 11.4 Hz)	6'-OCH ₃	56.2	3.51 (3H, s)
3'	44.3	3.71 - 3.70 (1H, m) 3.33 - 3.26 (1H, m)	12-OCH ₃	56.0	3.95 (3H, s)
4'	23.5	3.14 - 3.12 (1H, m) 3.06 - 2.98 (1H, m)	7-OH		8.44 (1H, br s)

化合物 **1** 与汉防己乙素 (**3**) 相比, C-3 位和 C-4 位的烷基碳信号 δ_c 44.6 (C-3)、 δ_c 22.1 (C-4) 缺失, 而多出两个羰基碳信号 δ_c 159.3 (C-3)、 δ_c 177.0 (C-4), 其余信号与化合物 **3** 基本一致。结

合化合物 **1** 的 HMBC 谱(图 2), H-5 (δ_H 7.29) 与 C-4 (δ_c 177.0) 相关, NCH₃ (δ_H 2.90) 与 C-3 (δ_c 159.3) 相关, H-1 (δ_H 4.81) 与 C-3 (δ_c 159.3) 相关, 确定了两个羰基碳的位置。

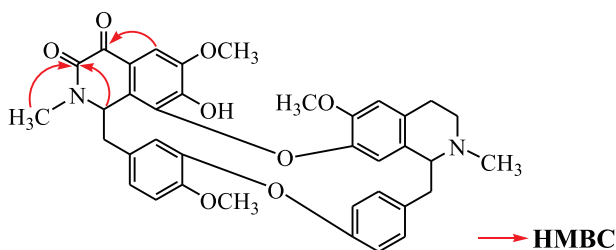


Figure 2 Key HMBC correlations of compound **1**

NOESY 谱(图 3)显示, H-1 与 NCH₃、H-10 存在相关信号, H-1' 与 N'CH₃、H-8'、H-14' 存在相关信号, 据此确定了化合物的相对构型。化合物 **1** 的绝对构型通过圆二色光谱(ECD)的实测图谱与计算图谱对比确定: 利用 Conflex 软件在 MMFF94S 分子力场对化合物 **1** 进行构象搜索, 采用 Gaussian 16 软件在 CAM-B3LYP/6-311 + G (d) 水平对筛选出的构象进行结构优化; 基于吉布斯自由能, 选择玻尔兹曼分布占比 $\geq 1\%$ 的稳定

构象进行 CAM-ECD 计算, 利用 SpecDis 1.7 软件根据玻尔兹曼权重拟合得到 ECD 计算图谱, 并与实验测得的 ECD 图谱进行对比分析。计算结果显示, 化合物 **1** 的 ECD 实测图谱与 1*S*, 1'*S* 构型的计算图谱基本吻合(图 3), 因此确定化合物 **1** 中手性碳的绝对构型为 1*S*, 1'*S*。综上, 鉴定化合物 **1** 为 3,4-二氧汉防己乙素, 经 SciFinder 检索为未见报道的新化合物。

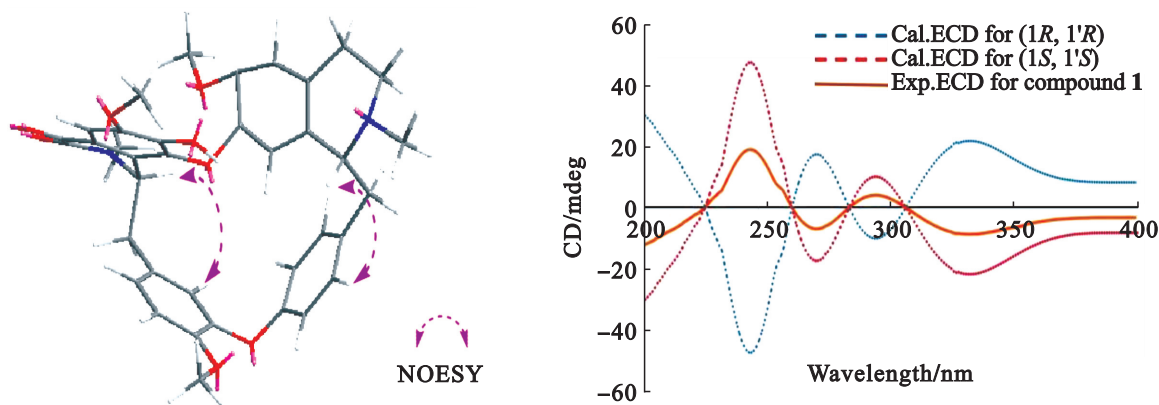


Figure 3 Key NOESY correlations and experimental and calculated ECD spectra of compound **1**

化合物 **2**: 白色针晶。 $[\alpha]_D^{25} = +207.0^\circ$ ($c = 0.01$, CHCl₃)。HR-ESI-MS m/z : 623.3107 [M + H]⁺ (计算值 623.3121, C₃₈H₄₃N₂O₆), 结合波谱数据确定化合物的分子式为 C₃₈H₄₂N₂O₆。 ¹H-NMR (600 MHz, CDCl₃) δ : 7.35 (1H, dd, $J = 8.2, 2.1$ Hz, H-14'), 7.14 (1H, dd, $J = 8.2, 2.5$ Hz, H-13'), 6.90 (1H, dd, $J = 8.2, 1.7$ Hz, H-14), 6.86 (1H, d, $J = 8.2$ Hz, H-13), 6.81 (1H, dd, $J = 8.2, 2.5$ Hz, H-11'), 6.54 (1H, d, $J = 1.7$ Hz, H-10), 6.51 (1H, s, H-5'), 6.33 (1H, s, H-5), 6.29 (1H, dd, $J = 8.2, 2.1$ Hz, H-10'), 5.99

(1H, s, H-8'), 3.93 (3H, s, 12-OCH₃), 3.92 ~ 3.89 (1H, m, H-1'), 3.77 (1H, d, $J = 10.2$ Hz, H-1), 3.75 (3H, s, 6-OCH₃), 3.56 ~ 3.48 (2H, m, H-3, 3'), 3.37 (3H, s, 6'-OCH₃), 3.29 (1H, dd, $J = 12.4, 5.6$ Hz, H- α'), 3.18 (3H, s, 7-OCH₃), 2.92 ~ 2.87 (4H, m, H-3, 4, 3', 4'), 2.78 (1H, dd, $J = 23.6, 10.2$ Hz, H- α), 2.77 ~ 2.73 (2H, m, H-4', α'), 2.62 (3H, s, N'CH₃), 2.53 (1H, d, $J = 13.9$ Hz, H- α), 2.52 ~ 2.48 (1H, m, H-4), 2.34 (3H, s, NCH₃)。 ¹³C-NMR (150 MHz, CDCl₃) δ : 153.9 (C-12'), 151.1 (C-6), 149.5 (C-11), 148.8

(C-6'), 148.4 (C-7'), 147.2 (C-12), 144.0 (C-8), 137.9 (C-7), 135.0 (C-9), 132.9 (C-9'), 132.7 (C-10'), 130.1 (C-14'), 128.2 (C-4a), 127.8 (C-8a'), 127.5 (C-4a'), 122.9 (C-11', 14), 122.0 (C-8a, 13'), 120.0 (C-8'), 116.2 (C-10), 111.6 (C-13), 112.7 (C-5'), 105.8 (C-5), 63.9 (C-1'), 61.5 (C-1), 60.4 (7-OCH₃), 56.2 (6'-OCH₃), 55.9 (6,12-OCH₃), 45.0 (C-3'), 44.3 (C-3), 42.4 (NCH₃), 42.3 (N'CH₃), 42.0 (C-α), 38.4 (C-α'), 25.0 (C-4'), 22.2 (C-4)。以上数据与文献[20]报道基本一致,故鉴定化合物**2**为汉防己甲素。

化合物**3**:白色针晶。 $[\alpha]_D^{25} = +198.0^\circ$ ($c = 0.01, \text{CHCl}_3$)。HR-ESI-MS m/z : 609.2953 [M + H]⁺ (计算值 609.2965, C₃₇H₄₁N₂O₆)。结合波谱数据确定化合物的分子式为 C₃₇H₄₀N₂O₆。¹H-NMR (600 MHz, CDCl₃) δ : 7.34 (1H, dd, $J = 8.2, 2.0$ Hz, H-14'), 7.13 (1H, dd, $J = 8.2, 2.5$ Hz, H-13'), 6.86 (1H, dd, $J = 8.2, 1.3$ Hz, H-14), 6.83 (1H, d, $J = 8.2$ Hz, H-13), 6.80 (1H, dd, $J = 8.2, 2.5$ Hz, H-10'), 6.57 (1H, d, $J = 1.3$ Hz, H-10), 6.51 (1H, s, H-5'), 6.32 (1H, dd, $J = 8.2, 2.0$ Hz, H-10'), 6.28 (1H, s, H-5), 6.05 (1H, s, H-8'), 4.98 (1H, s, 7-OH), 3.92 (3H, s, 12-OCH₃), 3.77 (1H, d, $J = 9.1$ Hz, H-1), 3.75 (3H, s, 6-OCH₃), 3.53 ~ 3.45 (2H, m, H-3, 3'), 3.23 (1H, dd, $J = 12.5, 5.7$ Hz, H-α'), 2.99 ~ 2.81 (3H, m, H-3', 4, 4'), 2.78 (1H, dd, $J = 23.4, 10.2$ Hz, H-α), 2.75 ~ 2.66 (2H, m, H-4', α'), 2.63 (3H, s, N'CH₃), 2.55 (1H, d, $J = 13.9$ Hz, H-α), 2.43 ~ 2.37 (1H, m, H-4), 2.32 (3H, s, NCH₃)。 ¹³C-NMR (150 MHz, CDCl₃) δ : 153.9 (C-12'), 149.5 (C-11), 148.9 (C-6'), 147.2 (C-12), 145.8 (C-6), 143.6 (C-7'), 141.8 (C-8), 135.1 (C-9'), 134.9 (C-7), 134.6 (C-9), 132.7 (C-10'), 130.2 (C-14'), 128.6 (C-4a'), 128.2 (C-8a'), 123.4 (C-4a, 8a), 122.9 (C-14), 122.0 (C-11'), 120.7 (C-8'), 120.3 (C-13'), 116.3 (C-10), 111.6 (C-13), 113.1 (C-5'), 104.9 (C-5), 63.9 (C-1'), 61.6 (C-1), 56.3 (6'-OCH₃), 56.2 (6,12-OCH₃), 45.4 (C-3'), 44.6 (C-3), 42.7 (NCH₃), 42.5 (N'CH₃), 42.0 (C-α), 37.9 (C-α'), 25.6 (C-4'), 22.1 (C-4)。以上数据与文献[21]报道基本一致,故鉴定化合物**3**为汉防己乙素。

化合物**4**:白色粉末。 $[\alpha]_D^{25} = +293.0^\circ$ ($c = 0.01, \text{CHCl}_3$)。HR-ESI-MS m/z : 619.2475 [M + H]⁺ (计算值 619.2444, C₃₇H₃₅N₂O₇)。结合波谱数据确定化合物的分子式为 C₃₇H₃₄N₂O₇。¹H-NMR (600 MHz, CDCl₃) δ : 8.60 (1H, d, $J = 5.6$ Hz, H-3'), 8.34 (1H, dd, $J = 8.5, 2.1$ Hz, H-10'), 7.63 (1H, d, $J = 5.6$, H-4'), 7.38 (1H, dd, $J = 8.5, 2.1$ Hz, H-11'), 7.03 (1H, dd, $J = 8.2, 1.4$ Hz, H-14), 7.01 (1H, s, H-5'), 6.96 (1H, dd, $J = 8.5, 2.1$ Hz, H-14'), 6.92 (1H, dd, $J = 8.5, 2.1$ Hz, H-13'), 6.84 (1H, d, $J = 8.2$ Hz, H-13), 6.81 (1H, s, H-8'), 6.37 (1H, s, H-5), 5.96 (1H, d, $J = 1.4$ Hz, H-10), 3.93 (3H, s, 12-OCH₃), 3.79 (3H, s, 6-OCH₃), 3.64 (3H, s, 6'-OCH₃), 3.54 ~ 3.48 (1H, m, H-3), 3.27 (3H, s, 7-OCH₃), 3.05 (1H, s, H-1), 2.93 ~ 2.87 (1H, m, H-4), 2.86 ~ 2.83 (1H, m, H-3), 2.75 ~ 2.68 (1H, m, H-α), 2.53 ~ 2.44 (1H, m, H-α), 2.35 (3H, s, NCH₃), 2.34 ~ 2.28 (1H, m, H-4)。 ¹³C-NMR (150 MHz, CDCl₃) δ : 195.2 (C-α'), 160.3 (C-1'), 155.5 (C-12'), 154.0 (C-11), 151.1 (C-12), 149.4 (C-6'), 147.1 (C-6), 147.0 (C-7'), 146.8 (C-8), 142.0 (C-3'), 138.0 (C-7), 135.1 (C-9'), 134.7 (C-14'), 134.6 (C-9), 130.2 (C-10'), 128.6 (C-4a'), 128.2 (C-8a'), 123.9 (C-11'), 123.4 (C-4a, 8a), 123.3 (C-13'), 122.9 (C-14), 121.0 (C-4'), 117.1 (C-10), 112.0 (C-8'), 111.1 (C-13), 105.0 (C-5'), 104.9 (C-5), 60.8 (C-1), 60.4 (7-OCH₃), 56.3 (6'-OCH₃), 56.0 (12-OCH₃), 55.8 (6-OCH₃), 44.5 (C-3), 42.5 (NCH₃), 41.0 (C-α), 22.1 (C-4)。以上数据与文献[22]报道基本一致,故鉴定化合物**4**为氧化防己碱。

化合物**5**:白色粉末。 $[\alpha]_D^{25} = +200.0^\circ$ ($c = 0.01, \text{CHCl}_3$)。HR-ESI-MS m/z : 657.2726 [M + H]⁺ (计算值 657.2749, C₃₈H₄₃N₂O₆Cl)。结合波谱数据确定化合物的分子式为 C₃₈H₄₂N₂O₆Cl。¹H-NMR (600 MHz, CD₃OD) δ : 7.58 (1H, dd, $J = 8.2, 2.4$ Hz, H-14'), 7.14 (1H, dd, $J = 8.4, 2.6$ Hz, H-11'), 7.02 (1H, dd, $J = 8.2, 2.4$ Hz, H-10'), 6.98 (1H, dd, $J = 8.4, 2.6$ Hz, H-13'), 6.92 (1H, d, $J = 2.6$ Hz, H-10), 6.87 (1H, s, H-8'), 6.85 (1H, d, $J = 8.2$ Hz, H-13), 6.82 (1H, dd, $J = 8.2, 2.6$ Hz, H-14), 6.49 (1H, s, H-5'), 6.20 (1H, s, H-5), 5.29 (1H, t, $J = 4.9$ Hz, H-1'), 4.06 ~

4.00 (1H, m, H-1), 3.93 (3H, s, 12-OCH₃), 3.91 (3H, s, 6-OCH₃), 3.78 (3H, s, 6'-OCH₃), 3.69 ~ 3.62 (1H, m, H-3'), 3.59 ~ 3.54 (1H, m, H-3'), 3.51 ~ 3.48 (1H, m, H-α'), 3.44 (3H, s, 7-OCH₃), 3.17 ~ 3.12 (1H, m, H-α'), 3.07 ~ 3.04 (1H, m, H-4'), 3.03 ~ 3.01 (1H, m, H-α), 2.94 ~ 2.90 (1H, m, H-4'), 2.89 (3H, s, N'CH₃), 2.87 (1H, dd, *J* = 14.7, 10.4 Hz, H-α), 2.81 ~ 2.77 (1H, m, H-4), 2.75 ~ 2.73 (1H, m, H-4), 2.72 ~ 2.69 (1H, m, H-3), 2.68 ~ 2.66 (1H, m, H-3), 2.44 (3H, s, NCH₃)。 ¹³C-NMR (150 MHz, CD₃OD) δ: 156.1 (C-12'), 152.7 (C-6), 150.1 (C-8), 149.3 (C-6'), 149.2 (C-12), 149.1 (C-11), 146.5 (C-7'), 139.5 (C-7), 136.8 (C-9), 133.9 (C-9'), 132.6 (C-14'), 132.4 (C-10'), 129.0 (C-8'), 128.0 (C-4a), 124.9 (C-8a), 124.5 (C-4a'), 123.4 (C-14), 122.5 (C-8a', 13'), 121.2 (C-11'), 116.4 (C-10), 113.9 (C-5'), 113.4 (C-13), 106.8 (C-5), 70.9 (C-1'), 68.8 (C-1), 63.8 (C-3'), 60.1 (7-OCH₃), 56.7 (12-OCH₃), 56.6 (6'-OCH₃), 56.4 (6-OCH₃), 49.8 (C-3), 45.6 (N'CH₃), 42.7 (NCH₃), 41.9 (C-α), 37.4 (C-α'), 23.8 (C-4'), 23.1 (C-4)。以上数据与文献[23]报道基本一致,故鉴定化合物 **5** 为 cycleanhomine chloride。

化合物 **6**: 淡黄色粉末。[α]_D²⁵ = +300.0° (*c* = 0.01, CHCl₃)。HR-ESI-MS *m/z*: 607.2795 [M + H]⁺ (计算值 607.2808, C₃₇H₃₉N₂O₆)。结合波谱数据确定化合物的分子式为 C₃₇H₃₈N₂O₆。 ¹H-NMR (600 MHz, CDCl₃) δ: 7.42 (1H, dd, *J* = 8.2, 2.1 Hz, H-14'), 7.03 (1H, dd, *J* = 8.2, 2.5 Hz, H-13'), 6.95 (1H, dd, *J* = 8.2, 1.4 Hz, H-14), 6.86 (1H, d, *J* = 8.2 Hz, H-13), 6.64 (1H, s, H-5'), 6.35 (1H, dd, *J* = 8.2, 2.1 Hz, H-10'), 6.34 (1H, s, H-5), 5.96 (1H, d, *J* = 1.4 Hz, H-10), 5.62 (1H, br s, -OCH₂O-), 5.57 (1H, s, H-8), 5.44 (1H, br s, -OCH₂O-), 4.24 ~ 4.21 (1H, m, H-1'), 3.89 (3H, s, 12-OCH₃), 3.70 (3H, s, 6-OCH₃), 3.42 ~ 3.37 (1H, m, H-3'), 3.23 ~ 3.15 (1H, m, H-1), 3.07 ~ 2.98 (1H, m, H-3), 2.95 ~ 2.92 (2H, m, H-3, 4'), 2.91 ~ 2.89 (2H, m, H-3', 4), 2.82 ~ 2.79 (1H, m, H-α'), 2.78 ~ 2.76 (1H, m, H-α), 2.75 ~ 2.70 (1H, m, H-4'), 2.66 (3H, s, N'CH₃), 2.58 (3H, s, NCH₃), 2.55 ~ 2.50 (3H,

m, H-4, α, α')。 ¹³C-NMR (150 MHz, CDCl₃) δ: 152.5 (C-12'), 148.9 (C-11), 148.8 (C-6), 147.4 (C-12), 147.1 (C-6'), 141.9 (C-7), 138.2 (C-9'), 137.2 (C-8'), 136.1 (C-7'), 133.0 (C-4a'), 132.7 (C-9), 131.8 (C-10'), 130.8 (C-4a), 128.4 (C-14'), 128.3 (C-8a), 126.7 (C-8a'), 124.0 (C-14), 122.5 (C-13'), 121.1 (C-11'), 117.9 (C-8), 116.7 (C-10), 111.2 (C-5, 13), 100.7 (-OCH₂O-), 64.2 (C-1), 62.0 (C-1'), 56.0 (12-OCH₃), 55.1 (6-OCH₃), 51.0 (C-3), 45.1 (C-3'), 43.8 (NCH₃), 42.1 (N'CH₃), 40.6 (C-α'), 37.9 (C-α), 29.2 (C-4), 25.3 (C-4')。以上数据与文献[24]报道基本一致,故鉴定化合物 **6** 为千金藤素。

化合物 **7**: 淡黄色粉末。[α]_D²⁵ = +206.0° (*c* = 0.01, CH₃OH)。HR-ESI-MS *m/z*: 637.2906 [M + H]⁺ (计算值 637.2914, C₃₈H₄₁N₂O₇)。结合波谱数据确定化合物的分子式为 C₃₈H₄₀N₂O₇。 ¹H-NMR (600 MHz, CDCl₃) δ: 8.32 (1H, s, NCHO), 7.24 (1H, dd, *J* = 8.2, 2.6 Hz, H-14'), 7.13 (1H, dd, *J* = 8.2, 2.6 Hz, H-13'), 6.83 (1H, s, H-5), 6.81 (1H, dd, *J* = 8.2, 2.2 Hz, H-14), 6.71 (1H, s, H-5'), 6.70 (1H, dd, *J* = 8.2, 2.6 Hz, H-11'), 6.40 (1H, d, *J* = 8.2 Hz, H-13), 6.32 (1H, dd, *J* = 8.2, 2.6 Hz, H-10'), 6.29 (1H, d, *J* = 2.2 Hz, H-10), 6.05 (1H, s, H-8'), 4.99 ~ 4.95 (1H, m, H-1'), 3.93 (3H, s, 12-OCH₃), 3.90 ~ 3.85 (1H, m, H-1), 3.77 (3H, s, 6-OCH₃), 3.68 (3H, s, 6'-OCH₃), 3.58 ~ 3.51 (1H, m, H-3'), 3.34 ~ 3.32 (1H, m, H-3), 3.26 ~ 3.23 (1H, m, H-4), 3.21 ~ 3.18 (1H, m, H-α'), 3.14 (3H, s, 7-OCH₃), 3.12 ~ 3.10 (1H, m, H-α), 3.04 ~ 3.00 (1H, m, H-α'), 2.99 ~ 2.95 (1H, m, H-3), 2.94 ~ 2.92 (1H, m, H-4), 2.84 ~ 2.80 (1H, m, H-4'), 2.65 ~ 2.62 (1H, m, H-3'), 2.61 ~ 2.58 (1H, m, H-α), 2.30 (3H, s, NCH₃)。 ¹³C-NMR (150 MHz, CDCl₃) δ: 161.9 (NCHO), 154.9 (C-12'), 151.8 (C-6), 150.5 (C-6'), 149.6 (C-11), 148.9 (C-8), 147.3 (C-12), 145.3 (C-7'), 137.4 (C-7), 132.9 (C-9'), 131.6 (C-10'), 130.3 (C-14'), 130.1 (C-8a'), 130.0 (C-8a), 126.8 (C-4a'), 126.1 (C-4a), 123.1 (C-14), 122.1 (C-5', 13'), 120.8 (C-9), 119.5 (C-8'), 116.1 (C-13), 111.8 (C-11'), 111.7 (C-5), 106.1 (C-10), 61.9 (C-1), 60.2 (7-

OCH₃), 56.2 (6', 12-OCH₃), 55.8 (6-OCH₃), 54.4 (C-1'), 43.6 (C-3), 42.5 (NCH₃), 41.3 (C-3'), 41.2 (C-α'), 38.6 (C-α), 29.3 (C-4'), 27.3 (C-4)。以上数据与文献[25]报道基本一致,故鉴定化合物**7**为(1R,1'S)-*N*-formylisotetrandrine。

化合物**8**:浅褐色粉末。 $[\alpha]_D^{25} = +233.0^\circ$ ($c = 0.01, \text{CHCl}_3$)。HR-ESI-MS m/z : 671.2909 $[\text{M} + \text{H}]^+$ (计算值 671.2888, C₃₉H₄₅N₂O₆Cl), 结合波谱数据确定化合物的分子式为 C₃₉H₄₄N₂O₆Cl。¹H-NMR (600 MHz, CDCl₃) δ : 7.50 (1H, dd, $J = 8.4, 2.3$ Hz, H-14'), 7.13 (1H, dd, $J = 8.4, 2.4$ Hz, H-13'), 6.86 (1H, dd, $J = 8.2, 1.5$ Hz, H-14), 6.85 (1H, d, $J = 8.2$ Hz, H-13), 6.80 (1H, dd, $J = 8.4, 2.4$ Hz, H-11'), 6.61 (1H, s, H-5'), 6.45 (1H, d, $J = 1.5$ Hz, H-10), 6.32 (1H, s, H-5), 6.31 (1H, dd, $J = 8.4, 2.3$ Hz, H-10'), 6.18 (1H, s, H-8'), 5.45 ~ 5.43 (1H, m, N'CH₂Cl), 5.42 ~ 5.39 (1H, m, H-1'), 5.34 ~ 5.28 (1H, m, N'CH₂Cl), 3.89 (3H, s, 12-OCH₃), 3.79 ~ 3.76 (1H, m, H-1), 3.74 (3H, s, 6-OCH₃), 3.67 (3H, s, N'CH₃), 3.61 ~ 3.58 (1H, m, H-3), 3.57 ~ 3.55 (1H, m, H-3'), 3.45 ~ 3.43 (1H, m, H-α'), 3.42 (3H, s, 6'-OCH₃), 3.37 ~ 3.33 (1H, m, H-α'), 3.25 (3H, s, 7-OCH₃), 2.96 ~ 2.94 (1H, m, H-3), 2.93 ~ 2.91 (3H, m, H-3', 4, 4'), 2.78 (1H, dd, $J = 15.2, 10.2$ Hz, H-α), 2.72 ~ 2.71 (1H, m, H-4'), 2.70 ~ 2.68 (1H, m, H-4), 2.53 (1H, d, $J = 5.2$ Hz, H-α), 2.38 (3H, s, NCH₃)。 ¹³C-NMR (150 MHz, CDCl₃) δ : 155.0 (C-12'), 151.2 (C-6, 6'), 149.3 (C-11), 148.0 (C-8), 147.5 (C-12), 145.3 (C-7'), 137.8 (C-7), 134.6 (C-9), 132.6 (C-14'), 131.2 (C-10'), 130.2 (C-9'), 128.7 (C-4a), 123.6 (C-4a'), 123.3 (C-14), 122.9 (C-8a), 122.8 (C-11', 13'), 120.5 (C-8'), 119.6 (C-8a'), 115.7 (C-10), 112.4 (C-5'), 111.8 (C-13), 106.3 (C-5), 69.0 (C-1'), 67.2 (N'CH₂Cl), 61.7 (C-1), 60.6 (7-OCH₃), 56.2 (12-OCH₃), 55.9 (6'-OCH₃), 55.8 (6-OCH₃), 52.9 (C-3'), 47.9 (N'CH₃), 43.4 (C-3), 42.3 (NCH₃), 42.0 (C-α), 36.5 (C-α'), 23.2 (C-4'), 21.9 (C-4)。以上数据与文献[26]报道基本一致,故鉴定化合物**8**为 *N*-chloromethyltetrandrine。

化合物**9**:浅褐色粉末。 $[\alpha]_D^{25} = -120.0^\circ$ ($c = 0.01, \text{CH}_3\text{OH}$)。HR-ESI-MS m/z : 639.3060

$[\text{M} + \text{H}]^+$ (计算值 639.3070, C₃₈H₄₃N₂O₇), 结合波谱数据确定化合物的分子式为 C₃₈H₄₂N₂O₇。¹H-NMR (600 MHz, CD₃OD) δ : 8.54 (1H, s, 7-OH), 7.49 (1H, dd, $J = 8.2, 2.3$ Hz, H-14'), 7.01 (1H, dd, $J = 8.2, 2.6$ Hz, H-13'), 6.83 (1H, d, $J = 8.0$ Hz, H-13), 6.79 (1H, dd, $J = 8.0, 2.2$ Hz, H-14), 6.73 (1H, s, H-5), 6.70 (1H, s, H-8'), 6.52 (1H, dd, $J = 8.2, 2.6$ Hz, H-11'), 6.46 (1H, dd, $J = 8.2, 2.3$ Hz, H-10'), 6.17 (1H, d, $J = 2.2$ Hz, H-10), 3.84 (3H, s, 12-OCH₃), 3.83 ~ 3.81 (1H, m, H-1'), 3.80 (3H, s, 7'-OCH₃), 3.78 ~ 3.73 (1H, m, H-1), 3.68 (3H, s, 6-OCH₃), 3.44 ~ 3.42 (1H, m, H-3), 3.38 (1H, dd, $J = 13.6, 1.8$ Hz, H-3'), 3.17 (1H, d, $J = 13.6$ Hz, H-α'), 3.10 (3H, s, 6'-OCH₃), 3.08 ~ 3.04 (1H, m, H-α), 2.95 ~ 2.92 (1H, m, H-3), 2.91 ~ 2.90 (1H, m, H-3'), 2.89 ~ 2.86 (1H, m, H-4), 2.83 ~ 2.77 (1H, m, H-4'), 2.69 (3H, s, N'CH₃), 2.67 (3H, s, NCH₃), 2.66 ~ 2.65 (1H, m, H-α'), 2.64 ~ 2.60 (1H, m, H-α), 2.56 ~ 2.54 (1H, m, H-4), 2.24 ~ 2.14 (1H, m, H-4')。 ¹³C-NMR (150 MHz, CD₃OD) δ : 154.4 (C-12'), 151.4 (C-7'), 148.5 (C-11), 147.2 (C-12), 147.0 (C-8a'), 146.1 (C-6), 140.9 (C-8), 137.5 (C-6'), 135.5 (C-9), 134.2 (C-9'), 133.3 (C-5', 7), 132.1 (C-14'), 131.5 (C-10'), 123.6 (C-4a), 123.0 (C-14), 122.8 (C-8a), 122.0 (C-4a'), 120.6 (C-13'), 120.5 (C-11'), 117.0 (C-10), 112.6 (C-13), 106.0 (C-8'), 105.5 (C-5), 66.4 (C-1'), 61.5 (C-1), 60.1 (6'-OCH₃), 56.9 (7'-OCH₃), 56.3 (6, 12-OCH₃), 49.5 (C-3'), 44.0 (N'CH₃), 43.9 (C-3), 42.4 (NCH₃), 41.4 (C-α'), 39.6 (C-α), 24.1 (C-4'), 22.1 (C-4)。以上数据与文献[27]报道基本一致,故鉴定化合物**9**为 thalrugosidine。

4 结果与讨论

本研究综合利用多种色谱分离技术,对粉防己的化学成分进行了研究,从中共分离鉴定出9个双苄基异喹啉类生物碱。其中,化合物**1**为新化合物,命名为3,4-二氧汉防己乙素,化合物**6,7**为首次从粉防己中分离得到,化合物**9**为首次从千金藤属植物中分离得到。本研究进一步丰富了粉防己的化学成分,为深入探究其药效物质基础提供了科学依据。

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Study on bisbenzylisoquinoline alkaloids from *Stephania tetrandra* S. Moore

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Abstract: To investigate the bisbenzylisoquinoline alkaloids from *Stephania tetrandra* S. Moore, various chromatographic and spectroscopic techniques were employed for the isolation, purification and structural identification of alkaloids from the 95% ethanol extract of *S. tetrandra*. Therefore, nine bisbenzylisoquinoline alkaloids were isolated, namely 3, 4-dioxoisotetrandrine (**1**), tetrandrine (**2**), fangchinoline (**3**), oxofangchirine (**4**), cycleahomine chloride (**5**), cepharanthine (**6**), (1*R*, 1'*S*)-*N*-formylisotetrandrine (**7**), *N*-chloromethyltetrandrine (**8**) and thalrugosidine (**9**). Compound **1** was a new compound, compounds **6** and **7** were isolated from this plant for the first time, and compound **9** was isolated from the *Stephania* genus for the first time.

Key words: *Stephania tetrandra* S. Moore; chemical constituent; structural identification; bisbenzylisoquinoline alkaloid