芪苈强心胶囊的化学成分研究(Ⅱ)

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[摘要] **目的**:研究复方中药芪苈强心胶囊的化学成分,从而明确芪苈强心胶囊的药效物质基础。**方法**:使用凝胶柱色谱、中低压液相色谱和制备高效液相色谱等手段,对芪苈强心胶囊大孔树脂 50% 和 10% 醇洗部分的化学成分进行分离和鉴定。**结果**:从这两段洗脱物中分离纯化得到 12 个单体化合物。利用 1D,2D 核磁共振光谱全部鉴定了其结构,分别为 5′,7-二羟基-3′-甲氧基异黄酮(**1**),人参皂苷 Rb_1(**2**),人参皂苷 Rf(**3**),人参皂苷 Re(**4**),2′-羟基-3′,4′-二甲氧基异黄烷-7-*O*-*β*-*D*-葡萄糖苷(**5**),芒柄花素 7-*O*-*β*-*D*-葡萄糖苷(**6**),(20R)-人参皂苷 Rh_1(**7**),8Z-decaene-4,6-diyne-1-*O*-*β*-*D*-glucopyranoside(**8**),杠柳毒苷(**9**),5-羟基-2-甲氧基-苯甲醇(**10**),腺苷(**11**),槲皮素-3-*O*-*β*-*D*-吡喃葡萄糖基-7-*O*-*β*-龙胆双糖苷(**12**)。**结论**:化合物 **1**,**5**~**12** 均为首次从芪苈强心胶囊中分离得到。其中化合物 **10** 为一个新的天然产物。

[关键词] 芪苈强心胶囊;化学成分;分离;核磁共振光谱
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Study of Chemical Components from Qili Qiangxin Capsule (Ⅱ)

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[**Abstract**] **Objective**: To study the chemical components of Qili Qiangxin capsule and to clear its material basis for efficacy. **Method**: The compounds were isolated from fractions eluted by 50% ethanol and 10% ethanol on sephadex LH-20, MPLC and PHPLC repeatedly. **Result**: Twelve compounds were isolated and their structures were elucidated on the basis of chemical methods and spectral analysis. They were identified as 5′, 7-dihydroxy-3′-methoxyisoflavone (**1**), ginsenoside Rb_1 (**2**), ginsenoside Rf (**3**), ginsenoside Re (**4**), 2′-hydroxy-3′, 4′-dimethoxy- isoflavane-7-*O*-*β*-*D*-glucoside (**5**), formononetin 7-*O*-*β*-*D*-glucopyranoside (**6**), (20R) - ginsenoside Rh_1 (**7**), 8Z-decaene-4, 6-diyne-1-*O*-*β*-*D*-glucopyranoside (**8**), periplocin (**9**), 5-hydroxy-2-methoxy-phenmerhylol (**10**), adenine riboside (**11**), quercetin-3-*O*-*β*-*D*-gluco- pyranosyl-7-*O*-*β*-gentiobioside (**12**). **Conclusion**: Compounds **1**, **5-12** are isolated from Qili Qiangxin capsule for the first time and compound **10** is a new natural product.

[**Key words**] Qili Qiangxin capsule; chemical components; isolate; NMR

中药复方是在中医药理论指导下,根据临床需 要,按照一定的组方原则与方法,由多种单味中药所

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形成的药物组合体。中药复方的作用就是由这个特定的组合体作用于机体所产生的,实质上是一种特定组合的化学物质组,而中药药效成分是复方发挥药效作用的物质基础,所以对复方中的化学成分,即药效物质基础的深入研究是中药现代化的关键和核心。芪苈强心胶囊是近年来在国内首先运用络病理论指导研发的治疗慢性充血性心力衰竭的中药新药,是中医药防治心血管疾病的重大创新,其组成为黄芪、附子、人参、丹参、葶苈子、泽泻、红花、玉竹、陈皮、桂枝、香加皮等 11 味中草药[1]。

本研究对芪苈强心胶囊 50% 和 10% 醇洗部分的化学成分进行了系统的分离和纯化。从中分离得到 12 个单体化合物,利用核磁共振光谱并参照文献数据,确定了它们的结构,化合物 **1**,**5** ~ **12** 均为首次从芪苈强心胶囊中分离得到。

1 材料

芪苈强心胶囊内容物由石家庄以岭药业提供,批号 110302。

核磁共振光谱由 Inova-SYS-600 型核磁波谱仪测定,质谱由 QTrap 3200 型质谱仪测定,IR 测定用 Bruker IFS-55 型红外分光光度计,薄层色谱硅胶由青岛海洋化工厂生产,反相材料 RP-18 为日本 YMC 公司生产,Sephadex LH-20 为 Amersham Pharmacia Biotech 生产,熔点仪为 YRT-3 型,温度未经校正,254,365 nm 紫外灯检测,10% 硫酸-乙醇溶液喷雾显色。

2 分离和纯化

芪苈强心胶囊内容物 500 g 溶于 5 L 蒸馏水中,药材质量浓度 0.4 g·mL^{-1},静置过夜滤去沉淀后上 AB-8 型大孔树脂柱,依次以水,10%,30%,50%,70%,95% 乙醇梯度各洗脱 5 倍柱体积(30 L),回收溶剂得到各段浸膏:10% 部分 39.8 g,30% 部分 23.6 g,50% 部分 19.2 g,70% 部分 4.7 g,95% 部分 3.7 g。500 g ODS 装中低压液相色谱柱,50% 醇洗部分浸膏 19.2 g 以 200 mL 甲醇溶解,每次 50 mL 上样,以乙腈-水系统梯度洗脱,合并同梯度流分。将收集到的组分分别以适宜的流动相条件进行制备高效液相分离纯化,得到化合物 **1**(4.27 mg),**2**(3.19 mg),**3**(5.24 mg),**4**(2.38 mg),**5**(6.23 mg),**6**(16.28 mg),**7**(1.97 mg),**8**(4.84 mg)和 **9**(96.31 mg)。10% 醇洗部分浸膏 39.8 g 以水溶解,过滤,上凝胶柱,以纯水洗脱,收集各段流出物,利用高效液相分析和制备得到化合物 **10**(1.72 mg),**11**(2.66 mg)和 **12**(6.28 mg)。

3 结构鉴定

化合物 **1** 棕色固体,ESI-MS 给出准分子离子峰 285[M + H]$^+$,分子式 $C_{16}H_{12}O_5$。^{1}H-NMR(600 MHz,CD_3OD)δ:8.06(1H,s,H-2),7.99(1H,d,J = 8.4 Hz,H-5),6.98(1H,brs,H-4′),6.91(2H,s,H-2′,6′),6.87(1H,d,J = 9.0 Hz,H-6),6.79(1H,s,H-8),3.82(3H,s,3′-OMe)。^{13}C-NMR(150 MHz,CD_3OD)δ:154.8(C-2),126.2(C-3),178.0(C-4),128.5(C-5),116.5(C-6),164.8(C-7),103.2(C-8),159.8(C-9),118.1(C-10),125.8(C-1′),112.6(C-2′),147.4(C-3′),117.4(C-4′),149.2(C-5′),121.6(C-6′),56.4(3′-OMe)。NMR 数据与文献报道的 5′,7-二羟基-3′-甲氧基异黄酮一致[2]。

化合物 **2** 淡黄色固体,mp 197 ~ 199 ℃,Liebermann-Burchard 反应呈阳性。^{13}C-NMR(150 MHz,CD_3OD)δ:40.2(C-1),27.2(C-2),91.3(C-3),40.6(C-4),57.6(C-5),19.2(C-6),35.9(C-7),41.0(C-8),51.1(C-9),37.9(C-10),30.8(C-11),70.2(C-12),49.7(C-13),52.4(C-14),31.5(C-15),27.2(C-16),52.9(C-17),17.4(C-18),16.7(C-19),85.0(C-20),22.5(C-21),36.8(C-22),23.9(C-23),126.0(C-24),132.2(C-25),26.0(C-26),16.3(C-27),28.4(C-28),16.7(C-29),18.0(C-30),104.5(3-Glc,C-1′),85.0(C-2′),78.5(C-3′),71.5(C-4′),78.5(C-5′),62.8(C-6′),105.4(2′-Glc,C-1″),77.7(C-2″),81.1(C-3″),71.6(C-4″),78.3(C-5″),62.8(C-6″),98.1(20-Glc,C-1‴),75.1(C-2‴),78.5(C-3‴),71.7(C-4‴),77.9(C-5‴),70.2(C-6‴),105.0(6‴-Glc,C-1⁗),75.2(C-2⁗),77.9(C-3⁗),71.9(C-4⁗),77.9(C-5⁗),63.1(C-6⁗)。NMR 数据与文献报道的人参皂苷 Rb_1 一致[3]。

化合物 **3** 无色结晶,Liebermann-Burchard 反应呈阳性,ESI-MS 给出准分子离子峰 801[M + H]$^+$。^{13}C-NMR(150 MHz,CD_3OD)δ:40.1(C-1),27.3(C-2),77.4(C-3),40.5(C-4),61.9(C-5),78.0(C-6),45.6(C-7),40.3(C-8),50.8(C-9),42.0(C-10),31.8(C-11),71.7(C-12),49.8(C-13),52.4(C-14),31.8(C-15),26.4(C-16),54.9(C-17),17.7(C-18),17.4(C-19),75.4(C-20),27.3(C-21),36.2(C-22),23.2(C-23),126.0(C-24),132.2(C-25),25.9(C-26),17.7(C-27),31.8(C-28),17.0(C-29),16.6(C-30),104.5(6α-Glc,C-1′),79.7(C-2′),77.7(C-3′),72.1(C-4′),79.9

(C-5′), 62.2 (C-6′), 102.4 (2′-Glc, C-1″), 74.5 (C-2″), 77.7 (C-3″), 72.1 (C-4″), 81.6 (C-5″), 62.7 (C-6″)。NMR 数据与文献报道的人参皂苷 Rf 一致[3]。

化合物 **4** 无色结晶, Liebermann-Burchard 反应呈阳性, ESI-MS 给出准分子离子峰 947 [M + H]$^+$。^{13}C-NMR (150 MHz, CD_3OD) δ: 40.3 (C-1), 27.5 (C-2), 78.2 (C-3), 40.4 (C-4), 61.4 (C-5), 74.9 (C-6), 46.1 (C-7), 42.0 (C-8), 50.3 (C-9), 40.3 (C-10), 30.9 (C-11), 69.7 (C-12), 49.4 (C-13), 52.5 (C-14), 31.8 (C-15), 27.3 (C-16), 53.1 (C-17), 17.7 (C-18), 17.5 (C-19), 84.9 (C-20), 22.8 (C-21), 36.6 (C-22), 24.2 (C-23), 125.9 (C-24), 132.3 (C-25), 25.9 (C-26), 18.0 (C-27), 32.0 (C-28), 17.3 (C-29), 17.2 (C-30), 101.6 (6α-Glc, C-1′), 79.2 (C-2′), 78.1 (C-3′), 72.5 (C-4′), 78.0 (C-5′), 63.1 (C-6′), 101.6 (6′-Rha, C-1″), 72.2 (C-2″), 71.9 (C-3″), 74.0 (C-4″), 69.7 (C-5″), 18.0 (C-6″), 98.3 (20-Glc, C-1‴), 75.4 (C-2‴), 79.8 (C-3‴), 71.2 (C-4‴), 79.1 (C-5‴), 62.5 (C-6‴)。NMR 数据与文献报道的人参皂苷 Re 一致[3]。

化合物 **5** 无色针状结晶, 10% 硫酸乙醇显紫色斑点, mp 163 ~ 165 ℃。^{1}H-NMR (600 MHz, CD_3OD) δ: 3.94 (1H, t, J = 10.2 Hz, H-2), 4.21 (1H, ddd, J = 10.2, 3.6, 1.2 Hz, H-2), 2.80 (1H, dd, J = 15.6, 4.8 Hz, H-4), 2.93 (1H, dd, J = 15.6, 4.8 Hz, H-4), 6.91 (1H, d, J = 8.4 Hz, H-5), 5.51 (1H, d, J = 6.6 Hz, H-6), 6.49 (1H, d, J = 2.4 Hz, H-8), 6.41 (1H, d, J = 8.4 Hz, H-5′), 6.76 (1H, d, J = 9.0 Hz, H-6′), 4.85 (1H, d, J = 7.2 Hz, H-1″), 3.65 (1H, dd, J = 10.2, 5.4 Hz, H-6″), 3.25 (3H, s, 3′-OMe), 3.24 (3H, s, 4′-OMe)。^{13}C-NMR (150 MHz, CD_3OD) δ: 71.0 (C-2), 33.5 (C-3), 31.3 (C-4), 117.8 (C-4a), 131.2 (C-5), 110.2 (C-6), 158.4 (C-7), 105.7 (C-8), 156.3 (C-8a), 122.8 (C-1′), 149.7 (C-2′), 137.9 (C-3′), 153.2 (C-4′), 104.4 (C-5′), 122.3 (C-6′), 102.5 (7-Glc, C-1″), 74.9 (C-2″), 78.0 (C-3″), 71.4 (C-4″), 78.1 (C-5″), 62.5 (C-6″), 61.1 (3′-OMe), 56.3 (4′-OMe)。NMR 数据与文献报道的 2′-羟基-3′, 4′-二甲氧基异黄烷-7-*O*-β-*D*-葡萄糖苷一致[4]。

化合物 **6** 无色针状结晶, 10% 硫酸乙醇显黑色斑点, 放置一段时间后变绿色。^{1}H-NMR (600 MHz, C_5D_5N) δ: 8.16 (1H, s, H-2), 8.10 (1H, d, J = 9.0 Hz, H-5), 7.42 (2H, d, J = 5.4 Hz, H-2′, 6′), 7.20 (1H, d, J = 2.4 Hz, H-8), 6.93 (2H, d, J = 8.4 Hz, H-3′, 5′), 5.05 (1H, d, J = 7.2 Hz, H-1″), 3.77 (3H, s, 4′-OMe)。^{13}C-NMR (150 MHz, C_5D_5N) δ: 155.2 (C-2), 125.3 (C-3), 177.9 (C-4), 128.3 (C-5), 117.1 (C-6), 163.6 (C-7), 104.9 (C-8), 159.3 (C-9), 120.2 (C-10), 125.6 (C-1′), 131.4 (C-2′), 114.9 (C-3′), 161.2 (C-4′), 114.9 (C-5′), 131.4 (C-6′), 101.8 (7-Glc, C-1″), 74.8 (C-2″), 77.9 (C-3″), 71.3 (C-4″), 78.4 (C-5″), 62.5 (C-6″)。NMR 数据与文献报道的芒柄花素-7-*O*-β-*D* 葡萄糖苷一致[5]。

化合物 **7** 无色羽状结晶, 10% 硫酸乙醇显紫色斑点, mp 257 ~ 260 ℃, Liebermann-Burchard 反应呈阳性。^{13}C-NMR (150 MHz, CD_3OD) δ: 40.2 (C-1), 28.1 (C-2), 79.1 (C-3), 40.5 (C-4), 61.8 (C-5), 77.7 (C-6), 45.4 (C-7), 41.9 (C-8), 50.9 (C-9), 40.4 (C-10), 31.9 (C-11), 71.7 (C-12), 48.6 (C-13), 52.6 (C-14), 31.4 (C-15), 26.9 (C-16), 50.9 (C-17), 17.3 (C-18), 17.5 (C-19), 74.6 (C-20), 22.8 (C-21), 43.3 (C-22), 22.3 (C-23), 125.9 (C-24), 130.9 (C-25), 25.9 (C-26), 17.8 (C-27), 31.9 (C-28), 16.1 (C-29), 17.3 (C-30), 105.6 (6α-Glc, C-1′), 75.5 (C-2′), 80.9 (C-3′), 71.9 (C-4′), 79.9 (C-5′), 62.9 (C-6′)。NMR 数据与文献报道的 (20R)-人参皂苷 Rh_1 一致[6]。

化合物 **8** 无色晶体, ESI-MS 给出准分子离子峰 311 [M + H]$^+$。^{1}H-NMR (600 MHz, CD_3OD) δ: 3.62 (1H, dt, J = 9.6, 6.4 Hz, H-1$_a$), 3.92 (1H, dt, J = 9.6、6.4 Hz, H-1$_b$), 1.76 (2H, t, J = 7.2 Hz, H-2), 2.44 (2H, t, J = 7.2 Hz, H-3), 5.45 (1H, m, H-8), 6.08 (1H, dq, J = 10.8, 6.4 Hz), 1.82 (3H, dd, J = 6.4, 1.8 Hz), 4.20 (1H, dd, J = 7.8 Hz, H-1′)。^{13}C-NMR (150 MHz, CD_3OD) δ: 67.8 (C-1), 28.4 (C-2), 15.4 (C-3), 83.6 (C-4), 64.6 (C-5), 78.1 (C-6), 71.1 (C-7), 108.6 (C-8), 114.5 (C-9), 14.9 (C-10), 103.0 (C-1′), 73.7 (C-2′), 76.5 (C-3′), 70.2 (C-4′), 76.6 (C-5′), 61.3 (C-6′)。NMR 数据与文献报道的 8*Z*-decaene-4, 6-diyne-1-*O*-β-*D*-glucopyranoside 一致[7]。

化合物 **9** 无色羽状结晶, 10% 硫酸乙醇显黑色斑点, ESI-MS 给出准分子离子峰 719 [M + Na]$^+$。^{13}C-NMR (150 MHz, CD_3OD) δ: 26.6 (C-1), 26.8 (C-2), 75.5 (C-3), 35.4 (C-4), 75.9 (C-5), 35.8 (C-6), 24.8 (C-7), 41.6 (C-8), 40.2 (C-9), 41.8 (C-10), 22.7 (C-11), 40.9 (C-12), 51.0 (C-

13),86.5(C-14),33.3(C-15),28.0(C-16),51.9(C-17),16.4(C-18),17.4(C-19),178.7(C-20),75.2(C-21),117.8(C-22),177.6(C-23),98.1(3-Cym,C-1′),36.2(C-2′),77.2(C-3′),83.5(C-4′),70.5(C-5′),18.7(C-6′),58.5(OMe),106.1(4′-Glc,C-1″),76.0(C-2″),78.6(C-3″),71.7(C-4″),77.9(C-5″),62.9(C-6″)。NMR 数据与文献报道的杠柳毒苷一致[8]。此化合物为一个甲型强心苷的结构,可能与芪芪强心胶囊的强心作用直接相关。

化合物**10** 淡黄色粉末,IR ν_{max}(KBr) cm^{-1}:3 400,1 600,1 580,分子式 $C_8H_{10}O_3$。^{1}H-NMR(600 MHz,DMSO-d_6)δ:6.83(1H,d,J = 7.8 Hz),6.75(1H,d,J = 1.8 Hz),6.66(1H,dd,J = 7.8,1.8 Hz),提示存在苯环 ABX 偶合系统,8.83(1H,brs,-OH),4.95(1H,brs,-OH),4.96(2H,s,O-CH_2-),3.72(3H,s,-O-CH_3)。^{13}C-NMR(150 MHz,DMSO-d_6)δ:135.2(C-1),146.3(C-2),114.2(C-3),117.1(C-4),146.4(C-5),111.9(C-6),55.7(-O-CH_3),62.6(O-CH_2-)。鉴定为 5-羟基-2-甲氧基-苯甲醇,为一个新的天然产物,其合成路线报道于 1924 年[9]。

化合物**11** 淡黄色粉末,10% 硫酸乙醇不显色,紫外 254 nm 下有暗斑。ESI-MS 给出准分子离子峰 268[M + H]$^+$,^{1}H-NMR(600 MHz,DMSO-d_6)δ:8.34(1H,s,H-8),8.13(1H,s,H-2),7.33(2H,s,NH_2),5.87(1H,d,6.6 Hz,H-1′)。^{13}C-NMR(150 MHz,DMSO-d_6)δ:152.3(C-1),149.0(C-4),119.3(C-5),156.1(C-6),139.9(C-8),87.9(C-1′),73.4(C-2′),70.6(C-3′),85.8(C-4′),61.6(C-5′)。NMR 数据与文献报道的腺苷一致[2]。

化合物**12** 淡黄色粉末,Molish 反应阳性。^{1}H-NMR(600 MHz,DMSO-d_6)δ:12.61(1H,brs,5-OH),7.65(1H,d,J = 1.8 Hz,H-2′),7.59(1H,dd,J = 8.4、1.8 Hz,H-6′),6.87(1H,d,J = 8.4 Hz,H-5′),6.78(1H,d,J = 1.8 Hz,H-8),6.51(1H,d,J = 1.8 Hz,H-6),5.48(1H,d,J = 7.2 Hz,H-1″),5.12(1H,d,J = 7.2 Hz,H-1‴),4.86(1H,d,J = 7.8 Hz,H-1⁗)。^{13}C-NMR(150 MHz,DMSO-d_6)δ:156.8(C-2),133.6(C-3),177.6(C-4),160.9(C-5),99.3(C-6),162.8(C-7),94.4(C-8),155.9(C-9),105.6(C-10),121.0(C-1′),116.5(C-2′),144.8(C-3′),148.6(C-4′),115.3(C-5′),121.6(C-6′),100.8(3-Glc,C-1″),74.1(C-2″),77.6(C-3″),69.9(C-4″),77.0(C-5″),60.9(C-6″),99.7(7-Glc,C-1‴),73.1(C-2‴),76.2(C-3‴),69.2(C-4‴),75.3(C-5‴),68.4(C-6‴),103.5(6‴-Glc,C-1⁗),73.4(C-2⁗),76.5(C-3⁗),70.1(C-4⁗),76.7(C-5⁗),61.0(C-6⁗)。NMR 数据与文献报道的槲皮素-3-*O*-*β*-*D*-吡喃葡萄糖基-7-*O*-*β*-龙胆双糖苷一致[10]。

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