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人参内生球毛壳菌株 RSQMK-9 的化学成分研究

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摘　要:从人参内生球毛壳菌株 RSQMK-9 的发酵培养物中提取分离得到 14 个代谢产物,通过波谱分析鉴定其结构分别为麦角甾醇(**1**)、4,6,8,22-四烯-3-酮-麦角甾烷(**2**)、啤酒甾醇(**3**)、9(11)-去氢麦角甾醇过氧化物(**4**)、alternariol(**5**)、大黄素甲醚(**6**)、3-吲哚甲酸(**7**)、2,3,4-三甲基-5,7-二羟基-2,3-二氢苯并呋喃(**8**)、2-氨基苯甲酰胺(**9**)、2-氨基苯甲酸(**10**)、3-甲基苔色酸(**11**)、甘露醇(**12**)、chaetoglobosin A(**13**)及 **5′**-epichaetovirdin A(**14**)。这些化合物均为首次从人参内生球毛壳菌中发现,而且化合物 **6** 为首次从该属真菌中分离到。海虾致死试验结果显示:10 μg/mL 浓度下,化合物 **13** 和 **14** 对丰年虾的致死率分别为 83.4% 和 54.3%。

关键词:人参;内生真菌;球毛壳菌;化学成分;*Artemia salina*;毒性

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Chemical Constituents from Endophytic Fungus *Chaetomium* sp. RSQMK-9 Isolated from *Panax ginseng*

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Abstract: 14 metabolites, namely ergosterol (**1**), ergosta-4,6,8,22-tetraen-3-one (**2**), cerevisterol (**3**), 9(11)-dehyo-ergosterol peroxide (**4**), alternariol (**5**), physcion (**6**), Indole-3-carboxylic acid (**7**), 2,3,4-trimethyl-5,7-dihydroxy-2,3-dihydrobenzofuran (**8**), anthranilamide (**9**), anthranilic acid (**10**), 3-methylorsellinic acid (**11**), mannitol (**12**), chaetoglobosin A (**13**) and 5′-epichaetovirdin A (**14**) were firstly isolated from the extract of fermentation broth of fungus *Chaetomium* sp. RSQMK-9, an endophyte of *Panax ginseng*. Their chemical structures were elucidated by spectroscopic methods, compound **6** was firstly isolated from the genus *Chaetomium*. The toxicities of compounds **13** and **14** were tested by brine shrimp bioassay, and the mortality rates of compound **13** and **14** against *Artemia salina* larvae were 83.4% and 54.3%, respectively, at the concentration of 10 μg/mL.

Key words: *Panax ginseng*; endophytic fungus; *Chaetomium* sp.; chemical constituents; *Artemia salina*; toxicity

植物内生菌近年来之所以受到人们的重视是因为人们逐渐认识到它们对寄主植物重要的生态学作用及其能够产生结构新颖多变,生物活性显著的次生代谢产物的巨大潜力。现在,内生菌被认为是一类开发潜力巨大的生物资源,尤其是从中可以发现各种生物活性的天然小分子化合物[1]。人参(*Panax ginseng*)为五加科名贵药用植物,作为中草药已经被使用了几千年,具有抗疲劳、减肥、抗肿瘤和抗氧化等多种保健功效[2]。虽然人参化学成分和药理活性研究很多,但是关于人参内生菌次生代谢产物的相关研究还很少,值得进一步研究开发其内生菌天然产物。在长期从药用植物内共生菌次生代谢产物中寻找新颖活性化合物过程中[3-6],我们对东北地区长白山产的野生人参中分离的一株内生真菌 RSQMK-9 的化学成分进行了研究,从该菌的发酵产物中分离得到 14 个化合物。在此,我们报道这些化合物的分离纯化和结构鉴定以及对海虾的细胞毒活性。

1　仪器与材料

熔点仪为 XRC-1 型显微熔点仪,温度计未校正。NMR 用 BrukerAM-400 和 Bruker DRX-500 型核

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磁共振仪测定(TMS 为内标);EI-MS:70 eV, Varian MAT 731, Varian 311A, AMD-402; ESI-MS: Finnigan Mat-Incos 50, LCQ(Finnigan)。

柱色谱填料:硅胶(青岛海洋化工厂);反相填料(Merck RP-18);凝胶填料 Sephadex LH-20(Amersham Biosciences, Uppsala, Sweden);大孔树脂填料 Amberlite XAD-16(Rohm & Hass, Paris, France);制备 TLC 板:Silica gel 60 GF_{254};TLC 在 254 nm 和 365 nm 紫外光显色,并用 10% 硫酸-乙醇溶液加热显色。其余试剂均为分析纯。

本实验所用的内生真菌(编号为 RSQMK-9)是从人参(*Panax ginseng*)根部的新鲜组织分离得到,经鉴定确定为球毛壳菌(*Chaetomium globosum*)。

2　实验方法

2.1　球毛壳菌株 RSQMK-9 的液体发酵

菌株在 PDA 培养基上 28 ℃活化培养 5 d,然后接种在液体培养基(氯化钙 0.2 g,磷酸二氢钾 0.1 g,氯化钾 0.05 g,硫酸镁 0.1 g,葡萄糖 20.0 g,蛋白胨 15.0g,1000 mL 水,pH7.0)。在 1000 mL 的三角瓶中加入 400 mL 液体培养基,在 26 ℃的摇床上 120 rpm 旋转震荡培养 8 d,然后用于提取分离。

2.2　化合物的提取分离

20 L 发酵产物经过滤后分别获得菌丝体和发酵液。菌丝在 50 ℃下烘干粉碎,用丙酮做溶剂超声提取 3 次,合并蒸干溶解在甲醇中,用环已烷脱脂处理后浓缩得到粗提取物 3.5 g,滤液经过吸附柱(polymeric resin Amberlite XAD-16),水洗除去盐和大分子水溶性物质,之后用甲醇洗脱得到非水溶性成分,浓缩后得到 5.6 g 提取物,然后将其悬浮于少量水后用石油醚和乙酸乙酯分别萃取 3 次,乙酸乙酯萃取相浓缩得 2.2 g 萃取物。经过 TLC 对照,乙酸乙酯萃取物和菌丝部分脱脂后提取物成分基本相同,故将它们合并起来得到总提取物。提取物经粗硅胶拌样后进行硅胶层析,用二氯甲烷-甲醇系统梯度洗脱,检测合并得到 5 个组分(Fr. 1 ~ Fr. 5),Fr. 2 ~ Fr. 4 分别经过反复的硅胶柱层析、RP-18、制备 HPLC、Sephadex LH-20 进行分离纯化得到化合物 1 ~ 14。

2.3　海虾致死活性测试

海虾致死活性采用微量滴定板法,采用丰年虾(*Artemiasalina*)幼虫作为测试生物[7]。在室温下,直径 1.8 cm,深 2 cm 的每个培养孔中装入 0.2 mL 的人造海水,每个孔中放入人工孵化的游动的丰年虾幼体 30 个。将化合物用 DMSO 溶解,定量加入到每个培养孔中,稀释到最终 10 μg/mL 浓度。对照只加 DMSO,每一处理重复三次。在室温下黑暗培养 24 h 后,在显微镜下计算每个槽中死亡的海虾个数,最后用以下公式计算致死率(M)。

$$M = [(A-B-N)/(G-N)] \times 100$$

其中:M = 24 h 后的致死率;A = 24 h 后的死亡总数;B = 24 h 后对照槽中的死亡总数;N = 在加入药剂之前的死亡数;G = 挑选用于测试的小虾总数。

3　实验结果

3.1　化合物结构鉴定

化合物 1　无色针状晶体(氯仿)。^{1}H NMR(500 MHz, $CDCl_3$) δ:3.64 (1H, m, H-3), 5.56 (1H, d, J = 4.2 Hz, H-6), 5.38 (1H, d, J = 6.0 Hz, H-7), 0.62 (3H, s, H-18), 0.96 (3H, s, H-19), 1.03 (3H, d, J = 6.4 Hz, H-21), 5.19 (1H, dd, J = 15.5, 8.0 Hz, H-22), 5.25 (1H, dd, J = 15.8 Hz, H-23), 0.93 (3H, s, H-25), 0.85 (3H, d, J = 6.0 Hz, H-27), 0.84 (3H, d, J = 6.0 Hz, H-28)。以上数据和常见的真菌代谢产物 ergosterol[8] 数据一致,进一步通过与麦角甾醇标准品比较确定其结构。

化合物 2　黄色粉末(氯仿)。^{1}H NMR ($CDCl_3$, 500MHz) δ:5.72 (1H, s, H-4), 6.01 (1H, d, J = 9.4 Hz, H-6), 6.60 (1H, d, J = 9.4 Hz, H-7), 0.95 (3H, s, H-18), 0.98 (3H, s, H-19), 1.05 (3H, d, J = 6.6 Hz, H-21), 5.21 (1H, m, H-22), 5.22 (1H, m, H-23), 0.82 (3H, d, J = 7.0 Hz, H-26), 0.84 (3H, d, J = 6.8 Hz, H-27), 0.92 (3H, d, J = 6.8 Hz, H-28); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 34.1 (C-1), 34.3 (C-2), 199.2 (C-3), 123.1 (C-4), 164.2 (C-5), 124.5 (C-6), 133.9 (C-7), 124.6 (C-8), 44.5 (C-9), 36.8 (C-10), 19.0 (C-11), 35.6 (C-12), 44.0 (C-13), 155.9 (C-14), 25.3 (C-15), 27.7 (C-16), 55.8 (C-17), 19.0 (C-18), 16.8 (C-19), 39.2 (C-20), 21.2 (C-21), 135.0 (C-22), 132.5 (C-23), 43.0 (C-24), 33.2 (C-25), 20.0 (C-26), 19.8 (C-27), 17.7 (C-28)。以上数据和文献报道一致[9],所以化合物被鉴定为 ergosta-4,6,8(14),22-tetraen-3-one。

化合物 3　无色针状晶体(氯仿)。^{1}H NMR ($CDCl_3$, 500 MHz) δ: 4.07 (1H, m, H-3), 3.62

(1H,d,J=4.8 Hz,H-6),5.35 (1H,dd,J=4.8,2.4 Hz,H-7),0.59 (3H,s,H-18),1.09 (3H,s,H-19),1.03 (3H,d,J=6.7 Hz,H-21),5.16 (1H,dd,J=15.4,8.0 Hz,H-22),5.23 (1H,dd,J=15.4,8.0 Hz,H-23),0.82 (3H,d,J=6.2 Hz,H-26),0.84 (3H,d,J=6.9 Hz,H-27),0.92 (3H,d,J=6.6 Hz,H-28);^{13}C NMR ($CDCl_3$,125 MHz) δ:32.8 (C-1),30.4 (C-2),67.2 (C-3),39.3 (C-4),75.9 (C-5),73.1 (C-6),117.3 (C-7),143.2 (C-8),43.2 (C-9),37.0 (C-10),22.0 (C-11),38.9 (C-12),43.6 (C-13),54.7 (C-14),22.9 (C-15),28.0 (C-16),55.9 (C-17),12.3 (C-18),18.4 (C-19),40.4 (C-20),19.6 (C-21),131.9 (C-22),135.3 (C-23),42.8 (C-24),33.1 (C-25),19.9 (C-26),21.1 (C-27),17.6 (C-28)。通过与文献中 NMR 数据比较[9],确定化合物为 cerevisterol。

化合物 4 白色晶体(氯仿)。EI-MS(m/z):426[M]$^+$,394,376,299,251,69;^{1}H NMR (600 MHz,$CDCl_3$) δ:3.98 (1H,m,H-3),6.35 (1H,d,J=8.4 Hz,H-6),6.54 (1H,d,J=8.4 Hz,H-7),5.48 (1H,m,H-11),0.78 (3H,s,H-18),1.19 (3H,s,H-19),1.05 (3H,d,J=6.8 Hz,H-21),5.21 (1H,dd,J=15.4,8.0 Hz,H-22),5.30 (1H,dd,J=15.3,7.4 Hz,H-23),0.84 (3H,d,J=6.5 Hz,H-26),0.81 (3H,d,J=6.2 Hz,H-27),0.98 (3H,d,J=6.8 Hz,H-28)。以上数据与文献报道的 9(11)-dehyoergosterol peroxide 一致[8],通过进一步和标准品比较 R_f 值(0.49,氯仿∶丙酮=8∶1) 确定化合物结构。

化合物 5 白色晶体(甲醇)。EI-MS m/z 258[M]$^+$; HR-ESI-MS m/z: 259.0607 [M+H]$^+$, calcd. for $C_{14}H_{11}O_5$ 259.0602);^{1}H NMR (600 MHz, DMSO-d_6) δ:2.63 (3H,s,H-Me),6.37 (1H,d,J=1.70 Hz,H-4),6.71 (1H,d,J=2.20 Hz,H-3′),6.62 (1H,d,J=2.20 Hz,H-5′),7.24 (1H,d,J=1.80 Hz,H-6),11.72 (OH),10.43(2OH);^{13}C NMR (125 MHz, DMSO-d_6) δ:138.0 (C-1),108.9 (C-1′),97.2 (C-2),152.5 (C-2′),164.6 (C-3),101.5 (C-3′),100.8 (C-4),158.3 (C-4′),165.4 (C-5),117.4 (C-5′),104.3 (C-6),138.2 (C-6′),164.0 (C-7),25.1 (C-8)。以上数据与文献报道一致[10],故鉴定化合物为 alternariol。

化合物 6 橘红色晶体(氯仿)。ESI-MS m/z 283[M-H]$^-$;^{1}H NMR (600 MHz, $CDCl_3$) δ:12.30 (1H,s,1-OH),7.61 (1H,s,H-4),7.36(1H,d,J=2.4 Hz,H-5),7.05 (1H,d,J=1.2 Hz,H-2),6.67 (1H,d,J=2.4 Hz,H-7),3.97 (3H,s,6-OMe),2.43 (3H,s,3-Me);^{13}C NMR (125 MHz,$CDCl_3$) δ:190.8 (C-9),182.0 (C-10),166.5 (C-6),165.2 (C-8),162.5 (C-1),148.4 (C-3),135.3 (C-4a),133.2 (C-10a),124.5 (C-2),121.3 (C-4),113.7 (C-9a),110.3 (C-8a),108.2 (C-5),106.8 (C-7),56.1 (6-OMe),22.2 (2-Me)。以上数据与文献报道数据一致[11]。故鉴定化合物为 physcion。

化合物 7 黄色晶体(甲醇)。^{1}H NMR (CD_3OD, 400 MHz) δ:10.96 (1H,br s,NH),7.92 (1H,s,H-2),8.06 (1H,dd, J=2.1,6.0 Hz,H-4),7.18 (2H,m,H-5,6),7.42 (1H,dd,J=2.1,6.4 Hz,H-7);^{13}C NMR (CD_3OD, 125 MHz) δ: 169.2 (COOH),133.2 (C-2),108.8 (C-3),121.9 (C-4),123.3 (C-5),122.3 (C-6),112.8 (C-7),127.5 (C-8),138.3 (C-9)。经过和数据库 antibase 以及文献中 Indole-3-carboxylic acid 数据比较确定化合物为 Indole-3-carboxylic acid[12]。

化合物 8 白色结晶(甲醇)。^{1}H NMR (C_5D_5N, 500MHz) δ:4.42 (1H,m,H-2),3.02 (1H,m,H-3),6.96 (1H,s,H-6),1.29 (3H,d,J=6.4 Hz,2-CH_3),1.23 (3H,d,J=6.6 Hz,3-CH_3),2.39 (3H,s,4-CH_3);^{13}C NMR(C_5D_5N,125 MHz) δ:86.5 (C-2),44.8 (C-3),111.8 (C-4),151.0 (C-5),104.4 (C-6),140.8 (C-7),139.8 (C-8),132.6 (C-9),21.1 (2-CH_3),19.6 (3-CH_3),12.2 (4-CH_3)。以上数据与文献报道一致[13],故鉴定化合物为 2,3,4-trimethyl-5,7-dihydroxy-2,3-dihydrobenzofuran。

化合物 9 白色结晶(甲醇)。EI-MS m/z 136[M]$^+$;ESI-MS m/z:137 [M+H]$^+$;^{1}H NMR (600 MHz,CD_3OD) δ: 6.74 (1H,d, J=6.8 Hz,H-3),7.19 (1H,t, J=16.0 Hz,H-4),6.58 (1H,t, J=16.0 Hz,H-5),7.51 (1H,d,J=7.0 Hz,H-6)。经过和数据库 antibase 以及文献中 anthranilamide 数据比较确定化合物为 anthranilamide[14]。

化合物 10 白色晶体(甲醇)。^{1}H NMR ($CDCl_3$, 500 MHz) δ:6.68 (1H,d,J=7.8 Hz,H-3),7.33 (1H,td,J=7.8,1.8 Hz,H-4),6.69 (1H,t,J=7.8 Hz,H-5),7.19 (1H,dd,J=7.8,1.8 Hz,H-6);^{13}C NMR ($CDCl_3$,125 MHz) δ:109.6 (C-1),151.1 (C-2),116.5 (C-3),135.1 (C-4),116.8 (C-5),132.1

(C-6),173.7 (-COOH)。通过比较化合物和标准品 anthranilic acid 在薄层色谱上的显色情况和 R_f 值[两种展开系统:正丁醇-醋酸-水(BAW)(4∶1∶5)上层;正己烷 6 mL,乙酸乙酯 3 mL,另加两滴冰醋酸]确定化合物为 anthranilic acid。

化合物 11　浅黄色晶体(甲醇)。ESI-MS *m/z* 183[M + H]$^+$, HR-ESI-MS (*m/z*: 183.0646 [M + H]$^+$, calcd. for $C_9H_{11}O_4$ 183.0652); ^{1}H NMR (600 MHz, CD_3OD) δ: 6.19 (1H, s, H-5), 2.44 (3H, s, 3-CH_3), 2.04 (3H, s, 6-CH_3)。以上数据和 antibase 中 3-methylorsellinic acid (2,4-dihydroxy-3,6-dimethyl-benzoic acid)以及文献中数据一致[15]。

化合物 12　无色结晶(甲醇)。ESI-MS *m/z*: 183[M + H]$^+$; ^{1}H NMR(DMSO-d_6, 600 MHz): δ3.37 (2H, ddd, *J* = 4.5, 5.6, 11.2 Hz), 3.45 (2H, ddd, *J* = 3.6, 8.5, 8.8 Hz), 3.57 (2H, t, *J* = 7.6 Hz), 3.60 (2H, dd, *J* = 11.0, 8.8, 3.6 Hz), 4.08 (2H, d, *J* = 7.0 Hz, OH), 4.26 (2H, t, *J* = 5.5 Hz, OH), 4.34 (2H, d, *J* = 5.6 Hz, OH)。以上数据通过和标准品在薄层色谱上比较进一步确定 mannitol。

化合物 13　黄色粉末(氯仿)。ESI-MS (*m/z*): 527[M-H]$^-$, 551 [M + Na]$^+$, 1055 [2M-H]$^-$, 1079 [2M + Na]$^+$, 573 [M + HCOO]$^-$, 1101 [2M + HCOO]$^-$; HR-ESI-MS (*m/z*: 529.2687 [M + H]$^+$, calcd. for $C_{32}H_{37}N_2O_5$ 529.2695); ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.03 (1H, s, H-2′), 3.75 (1H, br d, *J* = 6.0 Hz, H-3), 7.47 (1H, d, *J* = 7.6 Hz, H-4′), 1.88 (1H, d, *J* = 4.4 Hz, H-5), 7.12 [1H, t(dd), *J* = 8.4 Hz, H-5′], 7.18 [1H, t(dd), *J* = 8.4 Hz, H-6′], 2.73 (1H, d, *J* = 4.6 Hz, H-7), 7.34 (1H, d, *J* = 8.0 Hz, H-7′), 2.12 (1H, br d, *J* = 13.6 Hz, H-8), 2.94 (2H, dd, *J* = 14.0, 4.0 Hz, H-10α), 2.65 (1H, dd, *J* = 14.0, 7.5 Hz, H-10β), 1.14 (3H, d, *J* = 4.4 Hz, H-11), 1.26 (3H, s, H-12), 6.04 (1H, dd, *J* = 15.0, 10.0 Hz, H-13), 5.22 (1H, m, H-14), 2.23 (1H, br d, *J* = 15.0 Hz, H-15), 2.49 (1H, m, H-16), 0.97 (3H, d, *J* = 6.6 Hz, 16-CH_3), 5.54 (1H, d, *J* = 9.0 Hz, H-17), 1.23 (3H, s, 18-CH_3), 5.03 (1H, d, *J* = 4.4 Hz, H-19), 6.49 (1H, d, *J* = 16.6 Hz, H-21), 7.67 (1H, d, *J* = 16.6 Hz, H-22)。以上数据和文献中数据一致[16],确定化合物为 chaetoglobosin A。

化合物 14　黄色结晶(甲醇)。ESI-MS *m/z*: 433.1[M + H]$^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.59 (1H, s, H-1), 6.75 (1H, s, H-4), 6.25 (1H, d, *J* = 15.9 Hz, H-9), 6.68 (1H, dd, *J* = 15.9, 8.2 Hz, H-10), 2.27 (1H, m, H-11), 1.39 (2H, m, H-12), 0.89 (3H, t, *J* = 7.2, H-13), 1.64 (3H, s, 7-Me), 1.10 (3H, d, *J* = 6.6 Hz, 11-Me), 3.46 (1H, m, H-4′), 3.66 (1H, m, H-5′), 1.06 (3H, d, *J* = 6.6 Hz, H-6′), 1.04 (3H, d, *J* = 7.2, 4′-Me); ^{13}C NMR (400 MHz, DMSO-d_6) δ: 150.7 (C-1), 157.0 (C-3), 105.0 (C-4), 140.1 (C-4a), 109.8 (C-5), 183.1 (C-6), 87.3 (C-7), 164.8 (C-8), 111.0 (C-8a), 120.2 (C-9), 146.9 (C-10), 40.1 (C-11), 29.0 (C-12), 12.1 (C-13), 29.8 (7-Me), 19.1 (11-Me), 167.9 (C-1′), 125.8 (C-2′), 200.8 (C-3′), 50.5 (C-4′), 69.5 (C-5′), 21.4 (C-6′), 12.9 (4′-Me)。以上数据和文献中数据相似[17],确定化合物为 5′-epichaetovirdin A。

3.2　海虾致死活性测试结果

化合物 **13** 为毛壳属真菌产生的细胞松弛素类生物碱,该类生物碱被报道具有强烈的抗肿瘤,抗真菌等生物活性[18];化合物 **14** 属于真菌来源的 azaphilone 类色素,目前报道的天然 azaphilone 类化合物具有抗肿瘤,抗病原细菌等多种生物活性[19]。细胞毒活性测试结果显示: 10 μg/mL 浓度下,处理 24 h 后,化合物 **13** 对丰年虾幼虫显示了明显的毒性,致死率为 83.4%;化合物 **14** 也显示了中等强度的毒性,致死率为 54.3%。阳性对照化合物 ganodermanontriol 在该浓度下的死亡率为 91.2%。已经发现的这两类真菌代谢产物结构新颖多变,活性显著。值得通过扩大发酵规模、改变培养基组成、培养条件及加入激发子等手段来进一步提高其化学多样性,从中发现细胞毒性更强的新化合物。

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