

耳草属植物化学成分及药理活性研究进展

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摘要:对耳草属植物化学成分、药理作用研究进展进行了综述, 为该属植物进一步研究和开发利用提供参考。耳草属植物主要含有环烯醚萜类、黄酮类、萘醌类、三萜类、生物碱等化学成分, 该属植物具有抗肿瘤、调节免疫、肝保护、抑菌、抗炎、抗氧化等多种药理作用。

关键词:耳草属; 化学成分; 药理作用; 研究进展; 环烯醚萜; 黄酮

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Research Progress on Chemical Components and Pharmacological Activities of Genus *Hedyotis*

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Abstract: The research progress on chemical components and pharmacological activities of genus *Hedyotis* were reviewed to provide a reference for the further research and development. The genus *Hedyotis* contains iridoids, flavonoids, anthraquinones, triterpenes, alkaloids and other compounds. Pharmacological activities such as Anti-tumor, immune regulation, liver protection, anti-bacteria, anti-inflammatory and anti-oxidant had been reported.

Key words: Genus *Hedyotis*; chemical composition; pharmacological activity; review; iridoids; flavonoids

耳草属 (*Hedyotis*) 为茜草科 (*Rubiaceae*) 植物, 主要分布于热带和亚热带地区, 少数分布于温带。我国有耳草属植物 69 种 (包括 7 个变种), 主要分布于长江流域及其以南各省区, 北部极少^[1]。目前临床上常用白花蛇舌草、牛白藤、耳草的地上部分入药, 具有清热解毒、消肿止痛等功效, 用于感冒发热、咽喉肿痛、咳嗽、疮疖和蛇咬伤。其中白花蛇舌草 (*H. diffusa*) 具有良好的抗癌作用, 临床常辅助癌症治疗, 中国药典一部 (2010 年版) 附录收录的植物来源为茜草科植物白花蛇舌草 *Oldenlandia diffusa* (willd.) Roxb. 的干燥全草^[2]。

国内外对耳草属植物报道较多。目前从耳草属中分离出环烯醚萜类、黄酮类、萘醌类、三萜类、生物碱类、糖类等多种类型数百种化合物, 其中环烯醚萜类、黄酮类、萘醌类、生物碱类为该属植物的主要化学成分。药理学研究表明, 该属植物具有抗肿瘤、免疫调节、肝保护、抑菌、抗炎、抗氧化等多种生物活性。

关于耳草属植物化学成分与药理作用的研究, 目前, 仅见斯建勇^[3]等于 2007 年进行过综述, 本文在其基础上总结了 2007 年至今最新研究进展, 并补充了 2007 年之前发表而并未被其收录的部分化合物, 如 teneoside A、teneoside B、hedyotideaside、capitelline、hedyocapitelline、hedyocapitelline 等, 从而更全面深入的对耳草属植物进行介绍, 为其进一步研究和应用奠定基础。

1 化学成分

1.1 黄酮类

耳草属植物中含有多种黄酮类成分, 主要为黄酮醇及其苷类以及双黄酮类成分, 如槲皮素及其苷类成分、山奈酚及其苷类成分、水仙苷、穗花杉双黄酮等。从白花蛇舌草 (*H. diffusa*) 中分离得到 isoscutellarein、isoetin (**2**、**4**)^[4]; 3-methoxy-5, 7-dihydroxy-flavonol (**5**)^[5]; kaempferol (**6**)^[7,10]; kaempferol-3-*O*- β -D-glucopyranoside、kaempferol-3-*O*-(6''-*O*- α -L-rhamnoseyl)- β -D-glucopyranoside (**7**、**8**)^[7]; kaempferol-3-*O*-[2-*O*-(6-*O*-E-feruloyl)- β -D-

glucopyranosyl]- β -D-glucopyranoside (**9**)^[8]; kaempferol-3-O-[2''-O-(E-6'''-O-feruloyl)- β -D-glucopyranosyl]- β -D-galactopyranoside、kaempferol-3-O-[2-O-(6-O-E-feruloyl)- β -D-glucopyranosyl]- β -D-galactopyranoside (**10**、**11**)^[20]; kaempferol-3-O-(2-O- β -D-glucopyranosyl)- β -D-glucopyranoside (**12**)^[8]; kaempferol-3-O-(2-O- β -D-glucopyranosyl)- β -D-galactopyranoside (**13**)^[20]; quercetin (**15**)^[9,17]; quercetin-3-O- β -D-glucopyranoside (**16**)^[7]; quercetin-3-O-(2''-O-glucopyranosyl)- β -D-glucopyranoside (**17**)^[7]; quercetin-3-O-[2-O-(6-O-E-feruloyl)- β -D-glucopyranosyl]-

β -D-galactopyranoside (**18**)^[8]; quercetin-3-O-[2-O-(6-O-E-feruloyl)- β -D-glucopyranosyl]- β -D-glucopyranoside (**19**)^[8]; 5-hydroxy-6,7,3',4'-tetramethoxyflavone (**20**)^[9]; amentoflavone (**24**)^[11]。从金毛耳草 (*H. chrysotricha*) 中分离得到 rutin (**1**)^[31,33,48]; isoscutellarein (**2**)^[4]; quercetin (**15**)^[9,17]; nicotiflorin (**22**)^[31]; narcissin (**23**)^[31,48]。从丹草 (*H. herbacea*) 中分离得到 kaempferol-3-O-rutinoside (**14**)^[45]。从纤花耳草 (*H. tenellifloa*) 中分离得到 5,7,4'-trihydroxy flavonol-3-O- β -D-glucoside (**21**)^[34]。从该属植物分离得到的黄酮类成分化学结构如图 1 所示。

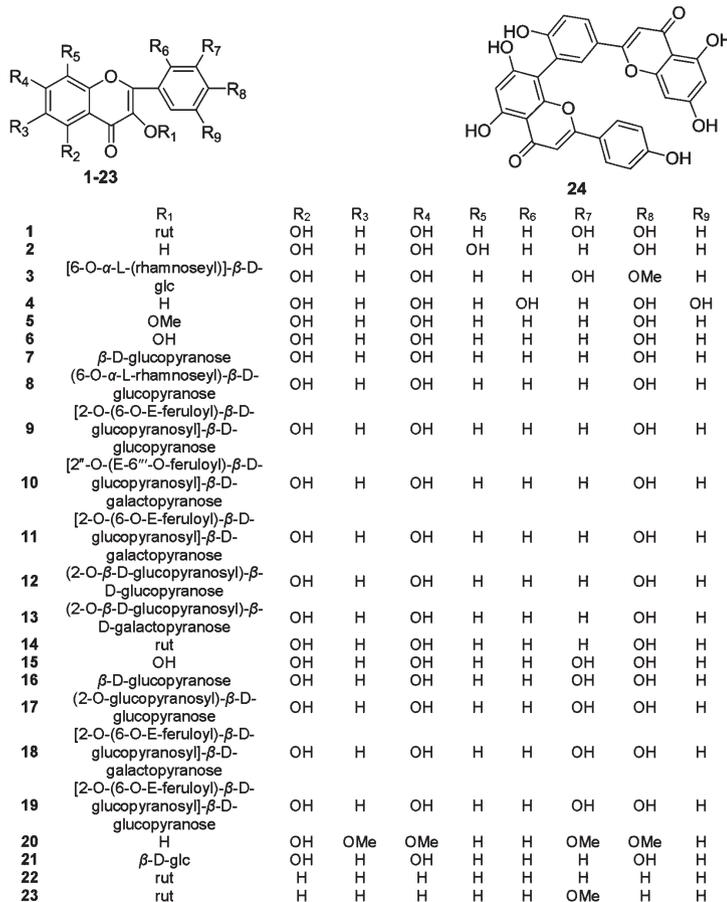


图 1 耳草属植物中黄酮类成分化学结构式

Fig. 1 Chemical structures of flavonoids from genus *Hedyotis*

1.2 环烯醚萜类

耳草属植物中含有的环烯醚萜类化合物主要为环烯醚萜苷,此类成分为耳草属植物特征化学成分,多数环烯醚萜类成分化学结构中 4 位羧基形成甲酯,也有少量 4 位无取代基,如 harpagoside、harpagide。从金毛耳草 (*H. chrysotricha*) 中分离得到 asperulosidic acid (**25**)^[48]; 10-deacetyl asperulosidic

acid (**27**)^[28]; scandoside methyl ester (**28**)^[31]; acetyl scandoside methyl ester (**29**)^[31]; 6 β -hydroxy-genipin (**30**)^[27]; asperuloside (hedyotiside B) (**32**)^[48]; deacetyl asperuloside (**33**)^[48]; hedyotiside B (6'-acetyl asperuloside) (**34**)^[28,31]; loganin、hedyoside、chrytosid、hedyotiside、hedyotideaside (**36-38**、**47**)^[48]; 6'-acetyl deacetyl asperuloside (**54**)^[31]。从白花蛇舌草

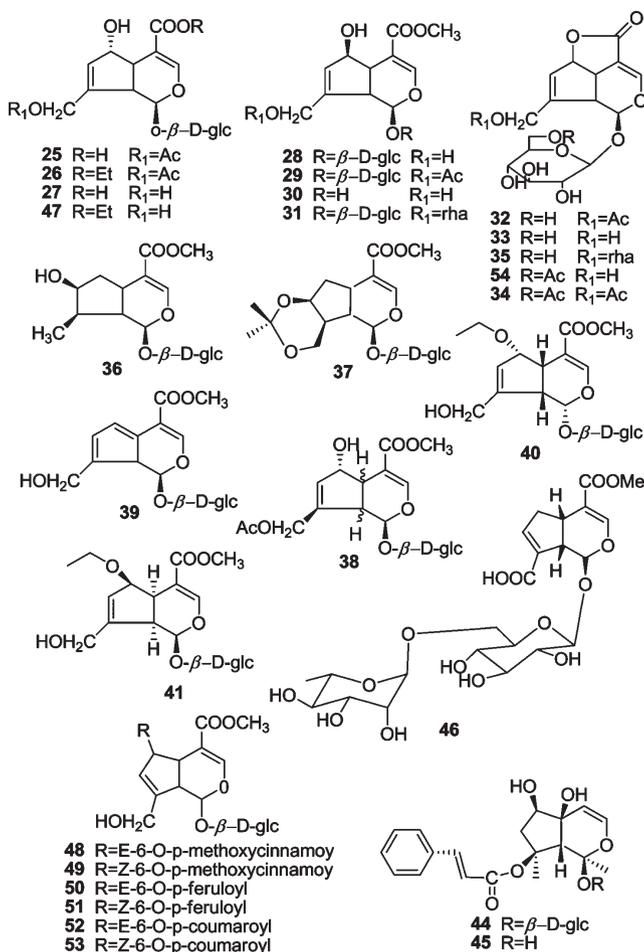


图2 耳草属植物中环烯醚萜类成分化学结构式

Fig. 2 Chemical structures of iridoids from genus *Hedyotis*

中分离得到 asperuloside (32)^[5,28]; diffusoside A、diffusoside B (40、41)^[13]; E-6-O-p-methoxy-cinnamoyl scandoside methyl ester、Z-6-O-p-methoxy-cinnamoyl scandoside methyl ester、E-6-O-p-feruloyl scandoside methyl ester、Z-6-O-p-feruloyl scandoside methyl ester、E-6-O-p-coumaroyl scandoside methyl ester、Z-6-O-p-coumaroyl scandoside methyl ester (48~53)^[21,23]。从纤花耳草 (*H. tenellifloa*) 中分离得到 asperulosidic acid (25)^[34]; teneoside A、teneoside B、deacetylasperuloside (31、33、35)^[47]; teneoside C、harpagoside、harpagide (42、44、45)^[35]。从该属植物中分离得到的环烯醚萜结构式见图2。

1.3 生物碱

从耳草属植物中分离得到的生物碱类成分多为 β-carboline 类和吲哚类生物碱。从黄毛耳草中分离得到 chrysotricine (55)^[31]; 从头状花耳草 (*H. capitellata*)

中分离得到 capitelline (58)^[42]、hedyocapitelline、hedyocapitine (56、57)^[41]、(-)-isocyclocapitelline、(+)-cyclocapitelline、isochrysotricine (59、60、61)^[38]。耳草属植物中生物碱类成分化学结构见图3。

1.4 醌类

据文献报道,目前从耳草属植物中分离得到的醌类成分多数为 9,10-蒽醌,另外还有少量 1,4-蒽醌和苯醌。取代基多为羟基、甲基、甲氧基和羟甲基,也有邻位环合成吡喃环的;从丹草 (*H. herbacea*) 中分离出 2-hydroxymethyl-10-hydroxy-1,4-anthraquinone、2,3-dimethoxy-9-hydroxy-1,4-anthraquinone、1,4-dihydroxy-2-hydroxymethyl anthraquinone、1,4-dihydroxy-2-hydroxymethyl anthraquinone (62、63、80、81)^[46]。从白花蛇舌草 (*H. diffusa*) 中分离得到 2-methyl-3-hydroxyanthraquinone、2-methyl-3-methoxy

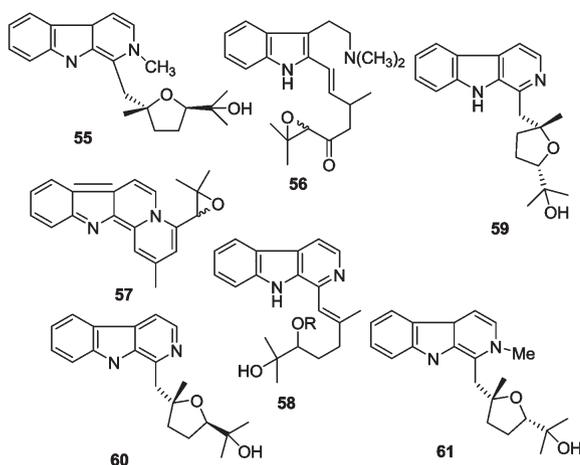


图3 耳草属植物中生物碱类成分化学结构式

Fig. 3 Chemical structures of alkaloids from genus *Hedyotis*

anthraquinone、2, 6-dihydroxy-3-methyl-4-methoxy anthraquinone (**66**、**67**、**75**)^[17]; 2-hydroxy-1-methoxy-anthraquinone、2-hydroxy-1, 3-dimethoxy anthraquinone (**68**、**70**)^[11]; 2-hydroxy-6-methyl-anthraquinone、2-hydroxy-3-methoxy-6-methyl-9, 10-anthraquinone (**73**、**78**)^[26]; 2-hydroxy-7-methyl-3-methoxy-anthraquinone (**69**)^[6]; 2, 3-dimethoxy-6-methyl anthraquinone (**71**)^[22]; 2-hydroxy-7-hydroxymethyl-3-methoxy anthraquinone (**72**)^[25]; 2, 7-dihydroxy-3-methyl-anthraquinone (**74**)^[14]; 2-hydroxy-1-methoxy-3-methyl-anthraquinone (**76**)^[6,16]; 2, 6-dihydroxy-1-methoxy-3-methyl-anthraquinone (**77**)^[16]; 1, 3-dihydroxy-2-methyl-anthraquinone (**87**)^[50]; 1, 7-dihydroxy-6-methoxy-2-methyl-anthraquinone (**88**)^[51]。从黄毛耳草 (*H. chrysotricha*) 中分离得到 2, 6-dimethoxy-1, 4-benzoquinone (**64**)^[31,48]; hydyotanthraquinone (**65**)^[32]。从头状花耳草 (*H. capitellata*) 中分离得到 2-hydroxymethyl-3, 4-[2-(1-hydroxy-1-methylethyl)-dihydrofuran]-8-hydroxyanthraquinone、capitellataquinone A、capitellataquinone B、capitellataquinone C、capitellataquinone D、rubiadin、anthragallol 2-methyl ether、alazarin 1-methyl ether、lucidin-3-*O*- β -glucoside (**79**、**89-97**)^[39]。从牛白藤 (*H. hedyotideia*) 中分离得到 hedanthrosides A、hedanthrosides B、hedanthrosides C、hedanthrosides D、hedanthrosides E (**82-86**)^[44]。从该属中分离得到的蒽醌类成分化学结构见图 4。

1.5 其他类

三萜类:从耳草属植物中分离得到的三萜类成

分主要为乌苏烷型、齐墩果烷型和羽扇豆烷型。从黄毛耳草分离得到 ursolic acid^[29]、oleanolic acid^[29]、betulic acid^[30]。从纤花耳草 (虾子草) (*H. tenellifloa*) 中分离得到 6 个乌苏烷类三萜化合物^[50]。从白花蛇舌草中分离得到 gypsogenic acid^[4]。从牛白藤中分离得到 epibetulinic acid^[48]。

甾体类:耳草属植物中分离得到的甾体类成分主要为植物甾醇。从白花蛇舌草、牛白藤、金毛耳草、纤花耳草中分离得到 β -sitosterol、stigmasterol、stigmasterol-5, 2-diene-3 β -7 α -diol、stigmasterol-5, 2-diene-3 β -7 β -diol、6-hydroxy stigmasterol-4, 22-dien-3-one、3-hydroxy stigmasterol-5, 22-diene-7-one、ergosterol、daucoesterol^[6,24,25,42,44]。

苯丙素类:从耳草属植物中分离得到的苯丙素类成分主要有简单苯丙素、香豆素和木脂素。从白花蛇舌草和金毛耳草中分离得到 esculetin、*p*-香豆酸、ferulic acid、caffeic acid、scopoletin、liriodendrin、iso-larisesinol、4, 4'-dihydroxy- α -truxillic acid、木脂体紫丁香脂素^[4,17,31,32,48,51]。从双花耳草 (*H. biflora*) 中分离得到角形吡喃香豆素 hedyotiscone A、hedyotiscone B、hedyotiscone C^[37]。

挥发性成分:从耳草属植物中分离的挥发油主要包括脂肪族含氧衍生物、芳香族含氧衍生物和萜类含氧衍生物。采用 SD、GC 和 GC/MS 鉴别出白花蛇舌草中 30 多种挥发性成分^[24]。采用 SD、SFE、GC/MS 从剑叶耳草 (*H. caudatifolia*) 中鉴别出 60 多种挥发性成分^[27]。

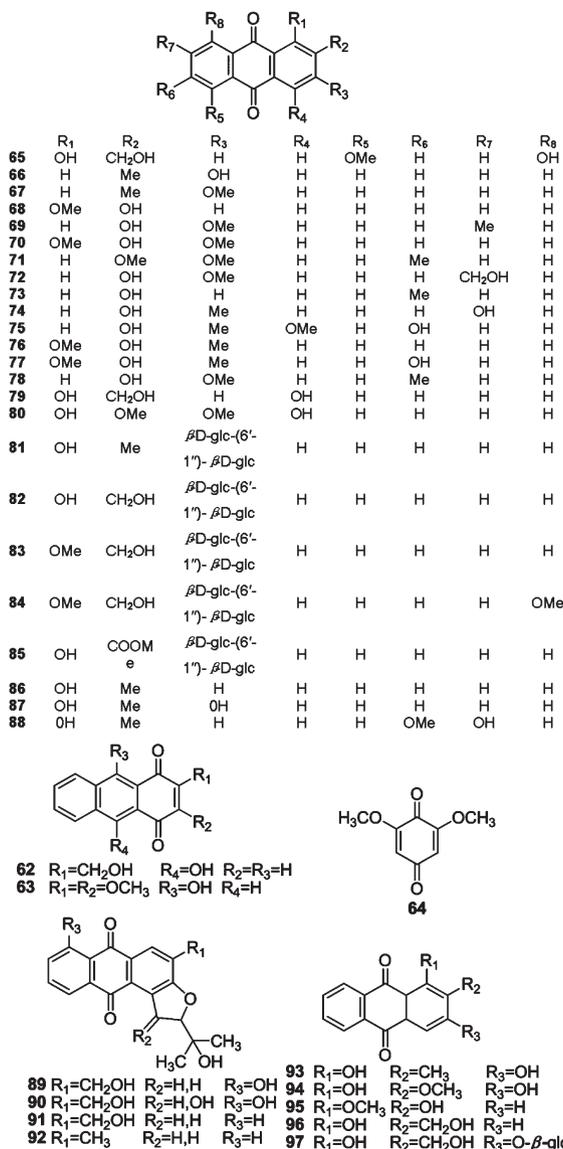


图4 耳草属植物中醌类成分化学结构式

Fig. 4 Chemical structures of anthraquinone from genus *Hedyotis*

2 药理作用

2.1 抗肿瘤作用

白花蛇舌草水煎液对宫颈癌 Hela 细胞有较好的抑制作用,可使 Ki-67 蛋白的表达下降^[51],降低端粒酶活性、下调 hTERT mRNA 的表达水平^[52]、使 Hela 细胞阻滞于 S 期^[53],从而诱导、促进肿瘤细胞的凋亡。白花蛇舌草多糖对宫颈癌 Hela 细胞也有较好的抑制作用^[54]。白花蛇舌草对肝癌具有治疗效果^[55],其水提取物通过上调 bax 蛋白表达^[56],提高 CD4⁺、CT8⁺ 淋巴细胞表达^[57],以及下调 Cdk2 和

E2F1 的 mRNA 表达,将肝癌细胞株 HepG2 细胞阻滞在 G0/G1 期^[58],从而达到对肝癌细胞的抑制作用。白花蛇舌草提取物可抑制结肠癌 HT-29 的细胞增殖,通过上调 bax,下调 bcl-2^[62]、耐药基因 ABCG2 的 mRNA^[63] 以及 HT-29 细胞 Pim-1 和 Pim-2 的 mRNA 表达^[64],从而诱导细胞凋亡,起到抗结肠癌的作用。白花蛇舌草提取物能明显抑制白血病 k562 细胞^[66]、CEM 细胞^[67]、多药耐药白血病细胞 HL-60/ADR^[68]、HL60 细胞株^[67] 生长,在一定浓度下,可观察到细胞缩小、染色质明显浓缩、核聚集等典型细胞凋亡特征,在琼脂凝胶电泳中出现明显的

DNA 梯形凋亡带,推测白花蛇舌草可能的抗白血病机制为诱导肿瘤细胞凋亡^[66]。

白花蛇色花草醇提取物对肺腺癌 A594 细胞具有一定的抑制作用,其机制可能是将细胞周期阻滞在 G₁-G₀ 期、上调 Bax 和下调 Bcl-2 的表达而诱导细胞凋亡^[65]。白花蛇舌草中豆甾醇类成分^[59]、挥发油类成分^[60]、黄酮类成分^[61] 对肝癌 H22、HepG2 具有一定的抑制作用。

2.2 对免疫功能的影响

白花蛇舌草多糖可显著促进溶血素形成、可使脾脏及胸腺增重并且明显提高吞噬能力,从而增强机体的免疫功能^[69]。白花蛇舌草总黄酮可以促进免疫功能低下的小鼠由 ConA 或 LPS- γ 诱导的脾淋巴细胞的增殖反应,促进免疫功能低下小鼠脾脏 IgM 抗体形成,并升高抗肿瘤药物所致的小鼠白细胞减少,从而增强机体免疫^[70]。

2.3 抗菌作用

白花蛇舌草 95% 乙醇提取物对革兰氏阳性菌、革兰氏阳性菌具有抑制作用,其中,对格兰氏阴性菌的抑菌作用大于革兰氏阳性菌^[71]。白花蛇舌草总黄酮对球菌和杆菌均具有不同程度的抑菌和杀菌作用,且对球菌的作用优于杆菌^[72]。头状花耳草提取物对枯草芽孢杆菌 B28 (突变株)、枯草芽孢杆菌 B29 (野生型)、铜绿假单胞菌、耐甲氧西林金黄色葡萄球菌有较好的抑制作用^[78]。

2.4 抗炎、镇痛作用

白花蛇舌草总黄酮对二甲苯诱导的小鼠耳肿胀和醋酸所致小鼠毛细血管通透性增高有一定的抑制作用,对大鼠松节油气囊肉芽增生和新鲜蛋清诱导大鼠足爪肿胀亦有明显的抑制作用,说明其具有一定的抗炎、镇痛作用^[72]。牛白藤石油醚、乙酸乙酯萃取物能明显减轻二甲苯诱导的小鼠耳肿胀程度,抑制热刺激和醋酸引起的小鼠疼痛反应,说明牛白藤有明显的抗炎、镇痛活性^[73]。

2.5 其它作用

保肝作用:白花蛇舌草可显著减轻 CCl₄ 引起的肝组织病理损伤程度,提高外周血 CD4⁺T 细胞的百分比和 CD4⁺T 细胞/CD8⁺T 细胞的比值,降低 CD8⁺T 细胞的百分比,降低血浆中 TNF- γ 和 IL-6 的水平,对肝损伤有一定的治疗作用^[74]。

治疗哮喘作用:白花蛇舌草通过阻断 NF- κ Bp65 表达,下调哮喘小鼠 BALF 中 IL-4、IL-5、IL-13 水平,同时上调 BAIF 中 IFN- γ 水平以及降低炎

症细胞数量,从而抑制气道炎症,达到治疗哮喘的作用^[75]。

抗氧化作用:白花蛇舌草多糖和总黄酮、丹草提取物均可以清除 DPPH 自由基,且氧化能力随着与浓度呈现量效关系^[76-78]。

神经保护作用:白花蛇舌草中的黄酮类和环稀醚萜类成分可减弱谷氨酸盐诱导的神经毒性,有一定的神经保护作用^[8]。

3 结语

耳草属植物具有丰富的植物资源和显著的药理作用,在民间大多作白花蛇舌草使用。目前,除了白花蛇舌草 (*Hedyotis diffusa* willd.) 外,对耳草属其它植物的研究与开发应用还较少,因此,亟待对本属植物的化学成分和药理作用进行进一步深入研究,从而阐明药效物质基础,为耳草属植物的进一步药用植物资源开发应用提供科学依据。

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