茵陈的化学成分、药理作用机制与临床应用研究进展

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摘　要:中药茵陈为菊科植物滨蒿(*Artemisia scoparia* Waldst. et Kit.)或茵陈蒿(*Artemisia capillaris* Thunb.)的干燥地上部分,具有清热利湿、利胆退黄等功效。其主要活性成分为香豆素类、黄酮类、有机酸类、挥发油等成分,调控信号通路,影响相关基因、蛋白或细胞因子的表达,发挥抗菌、抗炎、抗氧化等药理活性。本文通过检索来自 Pubmed、Web of science 等新近 30 年的国内外文献,对茵陈的化学成分、药理作用机制与临床应用等方面进行详细分类与系统总结,以期为茵陈的合理开发提供丰富的理论依据。

关键词:茵陈;滨蒿;茵陈蒿;构效关系;药理作用

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Research progress on chemical constituents, pharmacological mechanism and clinical application of Artemisiae Scopariae Herba

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Abstract: The dry overground part of *Artemisia scoparia* Waldst. et Kit. or *Artemisia Capillaris* Thunb. have the effect of clearing away heat and dampness, promoting gallbladder and retreating yellow. Their main chemical active components are coumarin, flavonoids, organic acids, volatile oil. It regulates the signaling pathway, affects the expression of related genes, proteins or cytokines, and exert antibacterial, anti-inflammatory, antioxidant and other pharmacological activities. Based on the research results reported in recent 30 years publications from Pubmed, Web of science and other databases, this review classified and summarized the chemical composition, pharmacological mechanism and clinical application of Artemisiae Scopariae Herba in detail, which can provide a rich theoretical basis for the rational development of Artemisiae Scopariae Herba.

Key words: Artemisiae Scopariae Herba; *Artemisia scoparia* Waldst. et Kit.; *Artemisia capillaris* Thunb.; structure-activity relationship; pharmaceutical activities

茵陈为菊科植物滨蒿(*Artemisia scoparia* Waldst. et Kit.)或茵陈蒿(*Artemisia capillaris* Thunb.)的干燥地上部分。茵陈最早记载于《神农本草经》,"主风湿寒热邪气,热结黄疸",其味微苦微辛,性微寒,入脾、胃、膀胱经,有清利湿热、利胆退黄等功效,主治黄疸尿少,湿温暑湿,闻疮瘙痒等症。茵陈主要含有香豆素类、黄酮类、有机酸类、挥发油类、萜类等化学成分。研究显示,其具有显著的保肝利胆作用、抗炎、抗氧化、抗肿瘤、抑菌和抗病毒等作用,临床主要用于治疗黄疸、母儿 ABO 血型不合、胆囊炎及肝内胆汁淤积症、阴道炎、治疗湿热型湿疹等。目前虽有学者对茵陈化学成分及其药理活性进行综述,但随着新成分的不断发现和药理活性的不断扩充,现有综述并不能对其"化学成分-药理作用机制-临床应用"进行全面的系统总结。本文对近年来国内外有关茵陈的"化学成分-药理作用机制-临床应用"的研究进展进行总结,以期为茵陈的合理开发提供科学依据和参考。

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1　化学成分

1.1　香豆素类化合物

茵陈中的香豆素类成分主要为简单香豆素和呋喃香豆素衍生物,除 isosabandin(**7**)与 sabandins B(**9**)属角型呋喃香豆素衍生物外,其余均属线型香豆素,其母核结构见图 1。茵陈中主要的香豆素类化合物及其结构分别见表 1、图 2。目前所发现的香豆素类化合物均在母核上进行取代,取代基有羟基(-OH)、甲氧基(-OCH_3)和甲基(-CH_3)等,常见于 C-6 位与 C-7 位取代,少数在 C-5 位、C-8 位取代,极少数以不饱和烃在 C-3 位取代茵陈素(**10**)。

香豆素类化合物治疗肝病、抗氧化和抗肿瘤等活性与抑制黄嘌呤氧化酶(xanthine oxidase,XO)具有密切的关系,有学者[1,2]通过模拟对接实验发现,香豆素母核内酯部位 C-2 位羰基和 C-1 位氧分别与 XO 的 Arg880 和 Thr100 以氢键的形式结合,6,7-二甲氧基香豆素(**1**)C-6 位羟基能与 E802 强结合,使香豆素类化合物与 XO 具有高亲和力。构效关系研究[2]表明母核上 C-5 位,C-7 位甲氧基及 C-6 位短链烃基的取代,能够有效地抑制促炎因子 iNOS 和 COX-2 的 mRNA 表达,下调 NO 的生成量,发挥抗炎的作用。C-6 位取代基在其药理活性上起重要作用:卤素或甲氧基取代后,抗肿瘤活性大大增强;C-6 位游离羟基是香豆素类化合物抗真菌活性所必须,而母核上 C-7 位甲氧基,C-6 位游离羟基和(或)C-8 位游离羟基是香豆素类化合物具有广谱抗菌活性的结构。

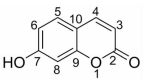

图 1　香豆素类化合物基本母核

Fig. 1　The basic parent structure of coumarins

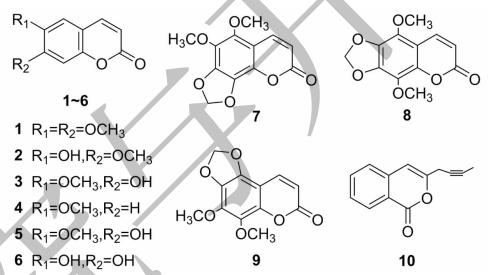

图 2　茵陈中香豆素类化合物结构

Fig. 2　The structure of coumarin compounds in Artemisiae Scopariae Herba

表 1　茵陈中香豆素类化合物

Table 1　Coumarin compounds in Artemisiae Scopariae Herba

序号 No.	化合物名称 Compound name	来源 Source	部位 Part	分子式 Formula	参考文献 Ref.
1	6,7-二甲氧基香豆素 6,7-Dimethylesculetin	*A. Capillaris*、*A. scoparia*	花蕾	$C_{11}H_{10}O_4$	3,4
2	7-Methylesculetin	*A. scoparia*	花序	$C_{10}H_8O_4$	5
3	6-Methylesculetin	*A. Capillaris*、*A. scoparia*	花序	$C_{10}H_8O_4$	5,6
4	6-甲氧基香豆素 6-Methoxycoumarine	*A. Capillaris*、*A. scoparia*	茎、叶	$C_{10}H_8O_3$	7
5	7-甲氧基香豆素 7-Methoxycoumarine	*A. capillaris*	茎、叶	$C_{10}H_8O_4$	4
6	6,7-二羟基香豆素 6,7-Dihydroxycoumarin	*A. capillaris*	幼苗	$C_9H_6O_4$	8
7	Isosabandin	*A. scoparia*	茎、叶	$C_{12}H_{10}O_6$	9
8	Sabandins A	*A. scoparia*	茎、叶	$C_{12}H_{10}O_6$	9
9	Sabandins B	*A. scoparia*	茎、叶	$C_{12}H_{10}O_6$	9
10	茵陈素 Capillarin	*A. Capillaris*、*A. scoparia*	花序	$C_{13}H_{10}O_2$	4,6

1.2　黄酮类化合物

茵陈的黄酮类化合物以普通黄酮类(**11**、**12**)、黄酮醇类(**13**、**22**)和黄酮氧苷(**24**、**36**)为主,有个别二氢黄酮类(**24**)和色原酮类(**25**)。黄酮类化合物具有 C_3-C_6-C_3 骨架结构,其基本母核结构见图 3,主要的黄酮类化合物见图 4、表 2。现代构效关系研究发现[10],黄酮类化合物的抗氧化能力,尤其是清除自由基能力与取代羟基的数量成正比,相邻取代羟基数目越多活性越强,且位于 A 环的羟基活性更大,而取代氧苷化或甲氧基化均会影响其活性。B 环存在 C-4 位羟基与 C 环 C-2 位、C-3 位双键及 C-3 位羟基取代的黄酮类化合物在茵陈保肝利胆的药理

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活性中起重要作用。黄酮氧苷因有羟基与糖基取代均具有一定的抗炎抑菌作用,经对比发现糖基对抑菌率的贡献大于羟基,而抗炎能力随糖基数目增加而增强。

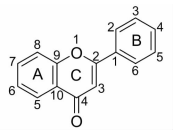

图 3 黄酮类化合物基本母核

Fig. 3 The basic parent structure of flavonoids compounds

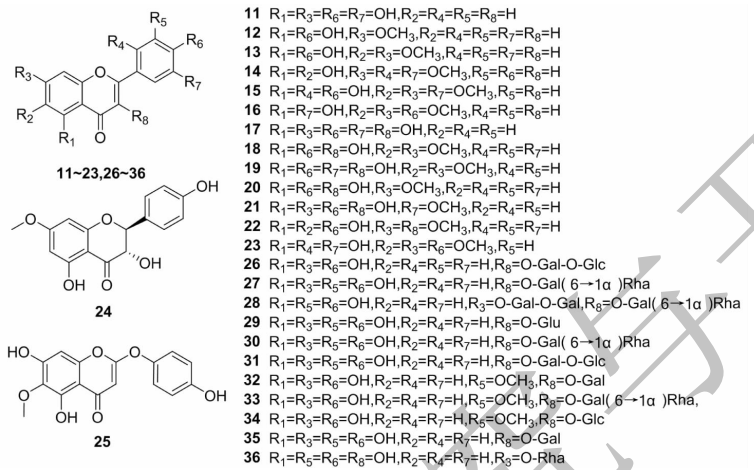

图 4 茵陈中黄酮类化合物结构

Fig. 4 The structure of flavonoids compounds in Artemisiae Scopariae Herba

表 2 茵陈中黄酮类化合物

Table 2 Flavonoids compounds in Artemisiae Scopariae Herba

序号 No.	化合物名称 Compound name	来源 Source	部位 Part	分子式 Formula	参考文献 Ref.
11	木犀草素 Luteolin	*A. scoparia*	花蕾	$C_{15}H_{10}O_6$	13
12	莞花素 Genkwanin	*A. capillaris*	茎、叶	$C_{16}H_{12}O_5$	4
13	蓟黄素 Circimaritin	*A. Capillaris*、*A. scoparia*	花序、花蕾、叶	$C_{17}H_{14}O_6$	5,6,11
14	异茵陈蒿黄酮 Isoarcapillin	*A. capillaris*	茎、叶	$C_{18}H_{16}O_8$	12
15	茵陈黄酮 Arcapillin	*A. Capillaris*、*A. scoparia*	花序、花蕾、叶	$C_{18}H_{16}O_8$	11,14
16	3′-甲氧基蓟黄素 Cirsilineol	*A. Capillaris*、*A. scoparia*	花蕾、叶	$C_{18}H_{16}O_7$	11
17	槲皮素 Quercetin	*A. Capillaris*、*A. scoparia*	花蕾	$C_{15}H_{10}O_7$	4,15,16
18	异泽兰素 Eupalitin	*A. scoparia*	花序	$C_{17}H_{14}O_7$	5
19	泽兰素 Eupatolitin	*A. Capillaris*、*A. scoparia*	花蕾	$C_{17}H_{14}O_8$	4,15
20	鼠李柠檬素 Rhamnocitrin	*A. Capillaris*、*A. scoparia*	花蕾、茎、叶	$C_{16}H_{12}O_6$	4,14,17
21	异鼠李素 Isorhamnetin	*A. Capillaris*、*A. scoparia*	花蕾	$C_{16}H_{12}O_7$	4,15
22	5,3′,4′-Trihydroxy-6,7-dimethoxyflavone	*A. scoparia*	花蕾	$C_{14}H_{17}O_7$	4,11
23	Isoarcapillin	*A. Capillaris*、*A. scoparia*	花蕾、茎、叶	$C_{18}H_{16}O_8$	4,13
24	7-Methylaromadendrin	*A. scoparia*	花序	$C_{16}H_{14}O_6$	5
25	茵陈色原酮 Capillarisin	*A. capillaris*	茎、叶	$C_{16}H_{12}O_7$	4
26	Kaempferol-3-glucogalactoside	*A. capillaris*	花蕾	$C_{27}H_{30}O_{16}$	15
27	Quercetin-3-*D*-robinoside	*A. scoparia*	茎、叶	$C_{27}H_{30}O_{16}$	4

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续表 2(Continued Tab. 2)

序号 No.	化合物名称 Compound name	来源 Source	部位 Part	分子式 Formula	参考文献 Ref.
28	Quercetin-3,7-rutinoso-digalactoside	*A. scoparia*	茎、叶	$C_{39}H_{50}O_{26}$	4
29	Quercetin-3-*O*-β-*D*-glucoside	*A. scoparia*	茎、叶	$C_{21}H_{20}O_{12}$	4
30	芦丁 Rutin	*A. scoparia*	茎、叶	$C_{27}H_{30}O_{16}$	4,16
31	Quercetin-3-glucogalactoside	*A. scoparia*	茎、叶	$C_{27}H_{30}O_{17}$	4
32	Isorhamnetin-3-*O*-β-*D*-galactoside	*A. scoparia*	茎、叶	$C_{22}H_{22}O_{12}$	4
33	Isorhamnetin-3-*O*-*D*-robinoside	*A. scoparia*	茎、叶	$C_{28}H_{32}O_{16}$	4
34	Isorhamnetin-3-glucoside	*A. scoparia*	茎、叶	$C_{22}H_{22}O_{12}$	4
35	Quercetin-3-*D*-galactoside	*A. scoparia*	花蕾、茎、叶	$C_{21}H_{20}O_{12}$	4,13
36	Quercetin-7-*O*-α-*L*-rhamnoside	*A. scoparia*	花蕾、茎、叶	$C_{21}H_{20}O_{11}$	4,13

1.3　有机酸类化合物

茵陈的有机酸类化合物多为酚酸类化合物,如绿原酸(**41**)、咖啡酸(**45**)等,具有明显的抗菌消炎等药理作用。主要有机酸类化合物见图 5、表 3。迄今为止的研究发现[18],有机酸类化合物能通过参与微生物能量竞争、改变细菌外膜通透性、改变渗透压及抑制生物合成等环节,发挥抑菌作用。茵陈所含有机酸的抑菌活性主要来自羧基和芳环的取代羟基。有机酸类化合物大多属于弱酸,由于酸性基团的数量、位置及吸、斥电子基团的影响,而具有不同的 pH 值和不同的细胞穿透能力,并影响细胞、微生物的多个生物代谢过程。

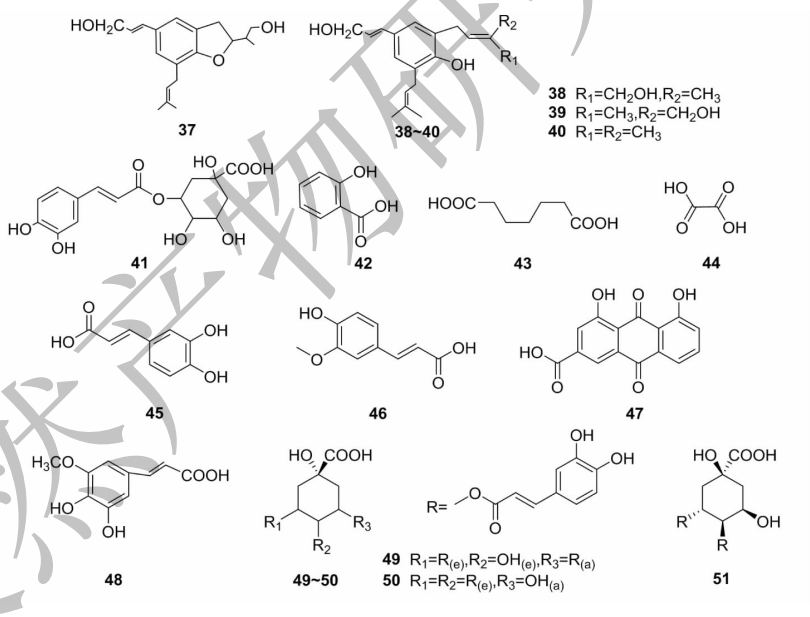

图 5　茵陈中有机酸类化合物结构

Fig. 5　The structure of organic acid compounds in Artemisiae Scopariae Herba

表 3　茵陈中有机酸类化合物

Table 3　The organic acid compounds in Artemisiae Scopariae Herba

序号 No.	化合物名称 Compound name	来源 Source	部位 Part	分子式 Formula	参考文献 Ref.
37	Artepilin A	*A. capillaris*	花序	$C_{19}H_{24}O_4$	6
38	Capilartemisin A	*A. capillaris*	茎、叶	$C_{19}H_{24}O_4$	12

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续表 3(Continued Tab. 3)

序号 No.	化合物名称 Compound name	来源 Source	部位 Part	分子式 Formula	参考文献 Ref.
39	Capilartemisin B	*A. capillaris*	花序	$C_{19}H_{24}O_4$	6
40	Artepilin C	*A. capillaris*	花序	$C_{19}H_{24}O_3$	6
41	绿原酸 Chlorogenic acid	*A. scoparia*	茎、叶	$C_{16}H_{18}O_9$	3,4
42	水杨酸 Salicylic acid	*A. scoparia*	茎、叶	$C_7H_6O_3$	4
43	杜鹃酸 Azelaic acid	*A. scoparia*	茎、叶	$C_9H_{20}O_4$	4
44	草酸 Oxalic acid	*A. scoparia*	茎、叶	$C_2H_2O_4$	4
45	咖啡酸 Caffeic acid	*A. Capillaris*、*A. scoparia*	花蕾、茎、叶	$C_9H_8O_4$	19
46	阿魏酸 Ferulic acid	*A. Capillaris*、*A. scoparia*	花蕾、茎、叶	$C_{10}H_{10}O_4$	19
47	大黄酸 Rhein	*A. Capillaris*、*A. scoparia*	花蕾、茎、叶	$C_{15}H_8O_6$	19
48	3,4-Dihydroxy5-methoxycinnaicacid	*A. scoparia*	茎、叶	$C_{10}H_{10}O_5$	20
49	3,5-*O*-Dicaffeoylquinic acid	*A. capillaris*	茎、叶	$C_{25}H_{24}O_{12}$	21,22
50	4,5-*O*-Dicaffeoylquinic acid	*A. capillaris*	茎、叶	$C_{25}H_{24}O_{12}$	21,22
51	3,4-*O*-Dicaffeoylquinic acid	*A. capillaris*	茎、叶	$C_{25}H_{24}O_{12}$	21,22

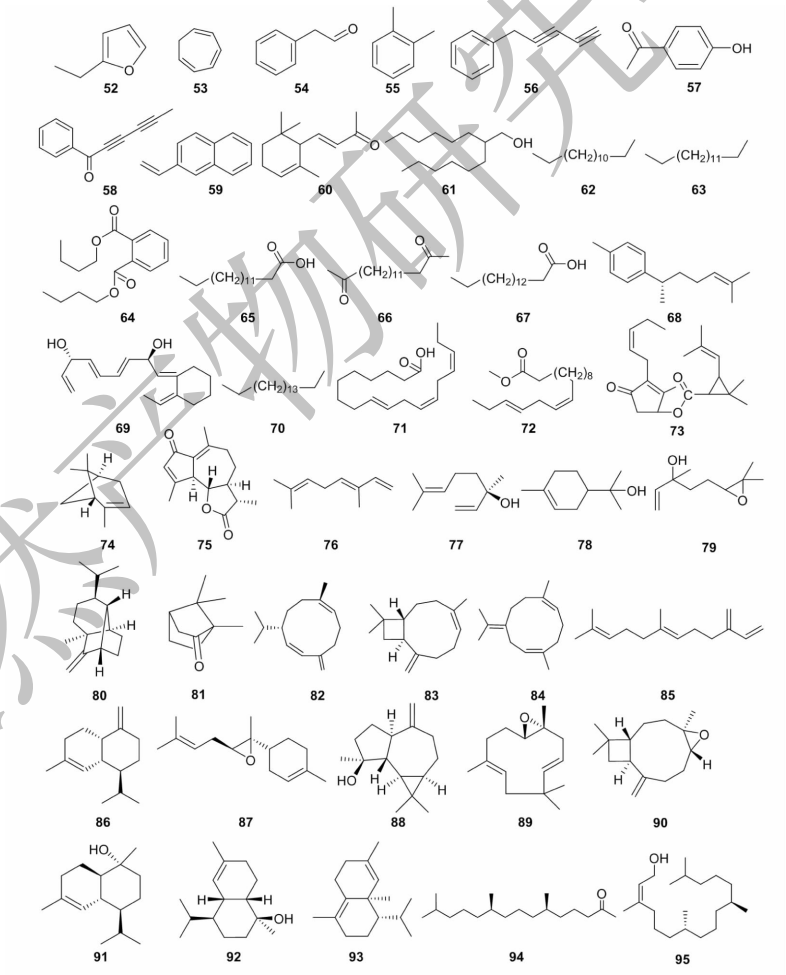

图 6 茵陈中挥发油及萜类化合物结构

Fig. 6 The structure of volatile oil and terpenoids in Artemisiae Scopariae Herba

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1.4　挥发油及萜类化合物

茵陈挥发油含量和色泽在不同时期[23],由幼苗期至成熟期逐渐增加,呈现不同的状态,在幼苗期色泽为绿色,含量约为0.031 mL/100 g,立秋时期色泽为棕色,含量约为0.47 mL/100 g,在花期时色泽为棕黄色,含量达到顶峰为0.96 mL/100 g。茵陈挥发油含大量萜类和色原酮、烯炔、醛酮等挥发组分,如茵陈二炔、茵陈炔酮、茵陈二炔酮等,是利胆的主要活性成分;烯炔、醛酮、长链脂肪醇等,因含有大量不饱和基团,是抗氧化、抗衰老的主要活性成分。茵陈中主要的挥发油及萜类化合物见图6、表4。

表4　茵陈中挥发油及萜类化合物

Table 4　The volatile oil and terpenoids in Artemisiae Scopariae Herba

序号 No.	化合物名称 Compound name	来源 Source	部位 Part	分子式 Formula	参考文献 Ref.	归属 Attribution
52	2-乙基呋喃 2-Ethyl furan	*A. capillaris*	茎、叶	C_6H_8O	24	挥发油
53	1,3,5-环庚三烯 1,3,5-Cycloheptatriene	*A. capillaris*	幼苗	C_7H_8	25	
54	苯乙醛 Phenylacetaldehyde	*A. capillaris*	茎、叶	C_8H_8O	24	
55	邻二甲苯 O-xylene	*A. capillaris*	幼苗	C_8H_{10}	25	
56	2,4-Pentadiynyl-benzen	*A. Capillaris*、*A. scoparia*	叶、幼苗	$C11H_8$	25-27	
57	4′-Hydroxyacetophenone	*A. capillaris*	茎、叶	$C_8H_8O_2$	4	
58	茵陈二炔酮 Capillin	*A. scoparia*	花蕾	$C_{12}H_8O$	13	
59	2-乙烯基萘 2-Vinylnaphthalene	*A. capillaris*	茎、叶	$C_{12}H_{10}$	24	
60	紫罗兰酮 Irisone	*A. capillaris*	茎、叶	$C_{13}H_{20}O$	24	
61	2-己基辛醇 2-Hexyl-1-octanol	*A. capillaris*	幼苗	$C_{14}H_{30}O$	25	
62	十四烷 Tetradecane	*A. capillaris*	幼苗	$C_{14}H_{30}$	25	
63	十五烷 Pentadecane	*A. capillaris*	幼苗	$C_{15}H_{32}$	25	
64	十五酸 Pentadecylic acid	*A. capillaris*	茎、叶、幼苗	$C_{15}H_{30}O_2$	28,29	
65	姜黄烯 Curcumene	*A. Capillaris*、*A. scoparia*	茎、叶、幼苗	$C_{15}H_{22}$	24-28	
66	邻苯二甲酸二丁酯 Dibutyl phthalate	*A. capillaris*	茎、叶、幼苗	$C_{16}H_{22}O_4$	24,25	
67	2,15-Hexacanedione	*A. capillaris*	茎、叶、幼苗	$C_{16}H_{30}O_2$	28,29	
68	棕榈酸 Palmitic acid	*A. capillaris*	茎、叶、幼苗	$C_{16}H_{32}O_2$	28,29	
69	镰叶芹二醇 Falcarindiol	*A. capillaris*	茎、叶、幼苗	$C_{17}H_{24}O$	28,29	
70	十七烷 Heptadecane	*A. capillaris*	幼苗	$C_{17}H_{36}$	25	
71	9,12,15-Octadecatrienoic acid	*A. capillaris*	茎、叶、幼苗	$C_{18}H_{30}O_2$	28,29	
72	亚麻酸甲酯 Methyl linolenate	*A. capillaris*	茎、叶	$C_{19}H_{32}O_2$	24	
73	茉酮菊素 I Jasmolin Ⅰ	*A. capillaris*	茎、叶	$C_{21}H_{30}O_3$	24	
74	β-蒎烯 β-pinene	*A. Capillaris*、*A. scoparia*	茎、叶	$C_{10}H_{16}$	24,28-30	萜类
75	乙酰氧母菊素 Leucodin	*A. capillaris*	茎、叶	$C_8H_8O_2$	31	
76	罗勒烯 Ocimene	*A. Capillaris*、*A. scoparia*	叶、幼苗	$C_{10}H_{16}$	26-28,30	
77	芳樟醇 Linalool	*A. Capillaris*、*A. scoparia*	茎、叶	$C_{10}H_{18}O$	24,26,27	
78	α-松油醇 α-terpineol	*A. Capillaris*、*A. scoparia*	茎、叶	$C_{10}H_{18}O$	24,26,27	
79	氧化芳樟醇 Linalool oxide	*A. Capillaris*、*A. scoparia*	茎、叶	$C_{10}H_{18}O_2$	24,26	
80	苜蓿烯 Sativen	*A. capillaris*	茎、叶、幼苗	$C_{15}H_{24}$	28,29	
81	樟脑 Camphor	*A. Capillaris*、*A. scoparia*	茎、叶	$C_{10}H_{16}O$	30	
82	大牻牛儿烯 D Germacrene D	*A. Capillaris*、*A. scoparia*	茎、叶、幼苗	$C_{15}H_{24}$	25,28-30	
83	石竹烯 Caryophyllene	*A. Capillaris*、*A. scoparia*	茎、叶、幼苗	$C_{15}H_{24}$	24-27,30	

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续表 4(Continued Tab. 4)

序号 No.	化合物名称 Compound name	来源 Source	部位 Part	分子式 Formula	参考文献 Ref.	归属 Attribution
84	乙酸异丁酯 1,5-Cyclodecadiene	*A. capillaris*	茎、叶	$C_{15}H_{24}$	24	
85	β-金合欢烯 β-farnesene	*A. capillaris*	幼苗	$C_{15}H_{24}$	25	
86	依兰油烯 γ-muurolene	*A. capillaris*	茎、叶	$C_{15}H_{24}$	24	
87	Trans-*Z*-α-bisabolene epoxide	*A. capillaris*	茎、叶、幼苗	$C_{15}H_{24}O$	28,29	
88	桉油烯醇 Spathulenol	*A. Capillaris*、*A. scoparia*	茎、叶	$C_{15}H_{24}O$	24,27	
89	Humulene epoxide II	*A. Capillaris*、*A. scoparia*	茎、叶	$C_{15}H_{24}O$	24,27	
90	氧化石竹烯 Caryophyllene oxide	*A. Capillaris*、*A. scoparia*	茎、叶	$C_{15}H_{24}O$	24, 26-29	
91	杜松醇 α-cadinol	*A. Capillaris*、*A. scoparia*	茎、叶	$C_{15}H_{26}O$	24,28-30	
92	τ-muurolol	*A. Capillaris*、*A. scoparia*	茎、叶、幼苗	$C_{15}H_{26}O$	28-30	
93	δ-杜松萜烯 δ-cadinene	*A. Capillaris*、*A. scoparia*	茎、叶	$C_{16}H_{26}$	24,30	
94	植酮 Phytone	*A. capillaris*	茎、叶	$C_{18}H_{36}O$	24	
95	植醇 Phytol	*A. capillaris*	茎、叶、幼苗	$C_{20}H_{10}O$	28,29	

2 主要药理活性及其相关机制

目前,茵陈药理活性研究较多报道集中在 6,7-二甲氧基香豆素、茵陈色原酮、绿原酸、茵陈二炔酮等单体化合物上,其他单体化合物研究报道甚少,更多研究停留在总提取物层面,且相关作用机制研究尚未深入报道。

2.1 保肝利胆作用

茵陈主归脾、胃、肝、胆经,清湿热、保肝、利胆退黄是其传统药用功能。现代药理研究发现 6,7-二甲氧基香豆素、6-methylesculetin、茵陈色原酮、绿原酸、β-蒎烯等化合物是其保肝利胆作用的物质基础。此外,茵陈还具有抗 ABO 血型不合和改善新生儿黄疸的辅助治疗作用。

2.1.1 脂肪肝

Shang[32] 通过脂多糖(lipopolysaccharide, LPS)刺激诱导小鼠腹腔巨噬细胞实验,发现茵陈中一种倍半萜内酯 leucodin,具有抑制巨噬细胞炎症反应并降低肝内脂肪蓄积的能力(机制见图 7)。

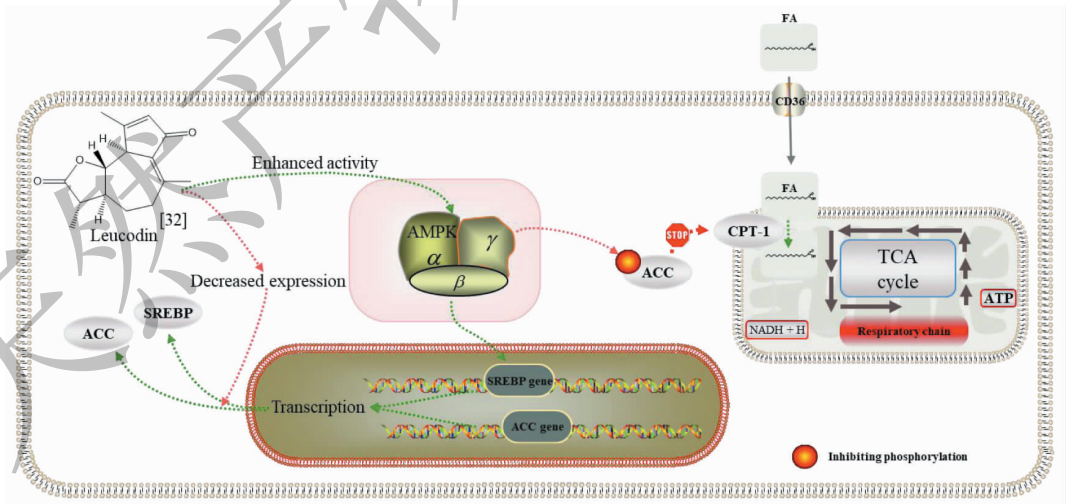

图 7 乙酰氧母菊素对 LPS 诱导的巨噬细胞的作用机制

Fig. 7 Mechanism of leucodin on LPS-induced macrophages

2.1.2 肝纤维化

肝星状细胞(hepatic stellate cell, HSC)的活化是肝纤维化的标志。Liu 等[33] 首次发现 6,7-二甲氧基香豆素能抑制 HSC-T6 细胞 $Smad_3$ 磷酸化水平,α-SMA、I 型胶原、III 型胶原和 NOX 的表达,从而抑制 HSC-T6 的活化和增殖,具有较好地治疗肝纤维

化的潜力(机制见图 8)。

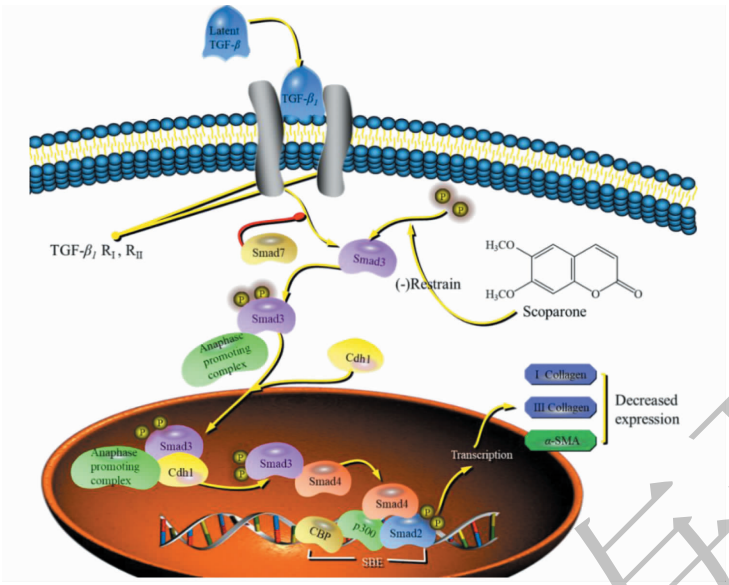

图 8　6,7-二甲氧基香豆素在 HSC-T6 细胞 TGF-β_1/Smad3 的调节过程

Fig. 8　Regulation of 6,7-dimethoxycoumarin in HSC-T6 cells TGF-β_1/Smad3

2.1.3　肝损伤

茵陈可以保护肝细胞膜,改善肝脏微循环,激活葡萄糖醛酸酶,通过直接作用于肝代谢酶系,减轻急性肝损伤反应。Zhang 等[35]报道,6,7-二甲氧基香豆素能显著地降低 CCl_4 致急性肝损伤大鼠模型血清中 ALT 活性及组织中 MDA 水平,且 6-methylesculetin、茵陈黄酮、茵陈色原酮对 $CC1_4$ 诱导肝毒性也具有治疗作用。Yang 等[36]、Gao 等[37]、Wang[38] 和 Liu 等[34]研究和报道茵陈水提物与茵陈挥发油在 CCl_4/EtOH 致急性肝损伤动物模型中,具有改善 ALT、AST、MDA、TG、GSH、GSH-Px、SOD、CAT、ALDH、ADH 水平的作用,增强肝脏抗损伤、抗氧化能力和清除乙醛的能力(相关机制见图 9)。

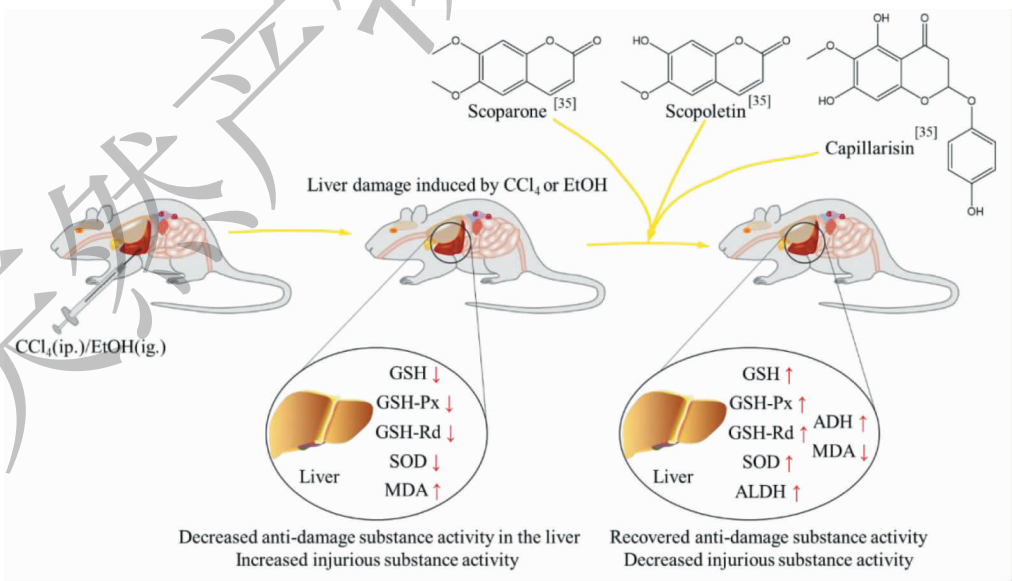

图 9　茵陈单体化合物对 CCl_4/EtOH 致肝损伤小鼠的保护作用

Fig. 9　Protective effects of monomer compounds of Artemisiae Scopariae Herba on liver injury induced by CCl_4/EtOH in mice

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2.2 抗炎作用

Tian[39]发现 Quercetin-7-*O*-α-*L*-rhamnoside 具有抑制巨噬细胞 RAW264.7 释放致炎因子一氧化氮(nitrous oxide,NO)并抑制炎症反应信号转导的活性。Ryu 等[40]和 Lu 等[41]研究发现 6,7-二甲氧基香豆素可通过 p38-MAPK 途径和 PI3K/Akt/NF-κB 通路,抑制促炎因子的表达与释放,具有预防治皮肤光老化和抗骨关节炎的能力。Khan 等[42,43]研究表明,茵陈色原酮也可作用于 NF-κB 通路,减少 iNOS、COX-2、TNF-α 的表达,腹腔注射茵陈色原酮还能显著抑制小鼠足底注射完全弗氏佐剂(complete Freund's adjuvant, CFA)引发的炎症反应。Nam 等[44]发现 3,5-*O*-dicaffeoylquinic acid 可降低 caspase-1 活性,显著下调胸腺基质淋巴生成素的表达水平,阻断 NF-κB 通路,改善肥大细胞介导的炎症性疾病,如特应性皮炎[45](机制见图 10)。

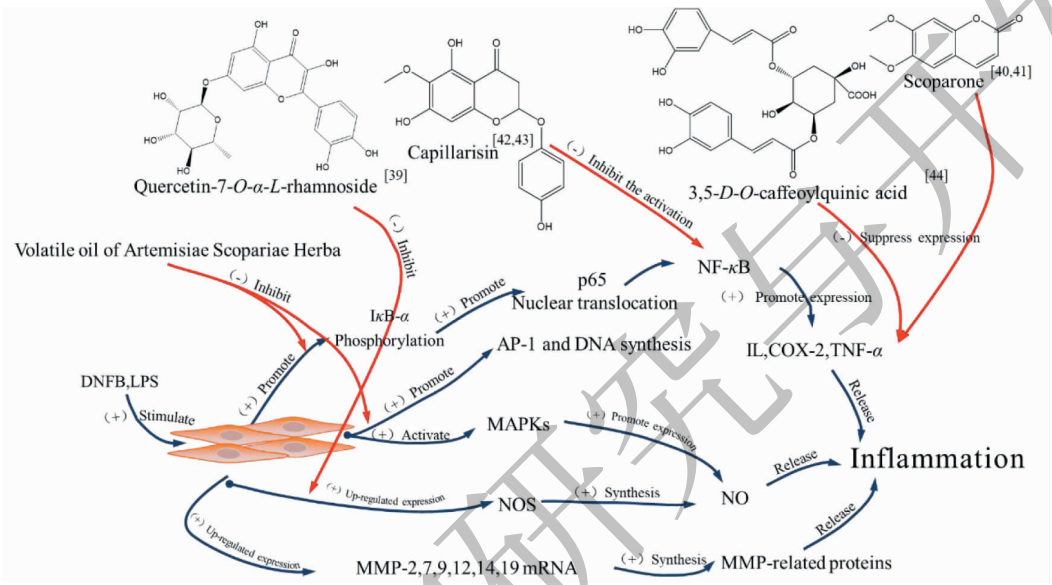

图 10 茵陈提取物及其单体组分对细胞炎症的调节机制

Fig. 10 The regulation mechanism of the extracts and monomer components of Artemisiae Scopariae Herba on cell inflammation

2.3 抗肿瘤作用

Wu[46]经过体外研究发现大黄酸具有抗 $HepG_2$ 肝癌细胞增殖作用,而绿原酸和大黄酸具有抗 ACHN 人肾癌细胞增殖作用。Liu[47]通过抗肿瘤实验发现 6,7-二甲氧基香豆素能影响 sacoma180 移植性 BALB/c 小鼠肿瘤模型 caspase-3 蛋白活性,增强 Bax 基因表达水平,具有强抑制作用。Jang 等[48]还发现 6,7-二甲氧基香豆素能通过抑制 IκB-α 磷酸化与抑制 NF-κB 亚基蛋白移位,从而降低 U937 细胞 IL-8 和单核细胞趋化蛋白 1(monocyte chemoattractant protein-1,MCP-1)的表达。Tsui 等[49]研究表明,茵陈色原酮通过调整抑癌基因 p21、p27 的表达,改变细胞周期蛋白(monocyte chemoattractant protein,Cyclin)D1、A 和 B 的表达量,并通过 IL-6/STAT3 通路,使癌细胞生长停滞,对前列腺癌细胞具有一定抑制作用。Masuda 等[50]、Cha 等[51]和 Lee 等[52]经细胞实验发现,茵陈二炔酮能激活 JNK 通路,HL-60 细胞线粒体释放细胞色素 C,诱导产生细胞毒性并导致细胞凋亡,由此推测茵陈二炔酮可能是一种潜在的抗癌药物。Wu 等[53]分离得到茵陈中的一种水溶性多糖(water-soluble polysaccharide, WACP),经实验证实 WACP 能使线粒体释放细胞色素 C 并活化 caspase-3、caspase-9 基因,诱导人鼻咽癌 CNE-2 细胞发生线粒体途径凋亡。Yan 等[54]发现茵陈乙酸乙酯部分也能改变线粒体膜电位,上调 caspase-3 表达水平,下调凋亡抑制基因 Survivin、XIAP、Mcl1 的表达,阻断 PI3K/AKT/mTOR 信号通路,诱导肝癌细胞(hepatoma carcinoma cell,HCC)凋亡,抑制其生长迁移。Jung 等[55]通过实验发现茵陈乙酸乙酯部分能降低缺氧诱导因子-1 和血管内皮生长因子(vascular endothelial growth factor, VEGF)的表达,抑制 HCC 的生长与血管生成。Jang 等[56]发现茵陈提取物能够通过 IL-6/$STAT_3$ 途径,对 HCC 和 W4P-NIH3T3 起抑制作用。Kim[57]等研究发现茵陈氯仿部位主要成分樟脑和冰片对 7,12-二甲基苯并蒽(dimethylbenzanthracene,DMBA)诱发小鼠表皮皮肤

癌具有强烈的抑制作用。Woo 等[58]经过实验表明茵陈乙醇部分能通过下调酪氨酸酶(tyrosinase,TYR)、酪氨酸酶相关蛋白-1、-2(tyrosinase-associated proteins -1 and -2,TRP-1 and -2)等黑色素特异性蛋白的表达,抑制 α-MSH 诱导 B16F10 黑素瘤细胞的增殖(机制见图 11)。

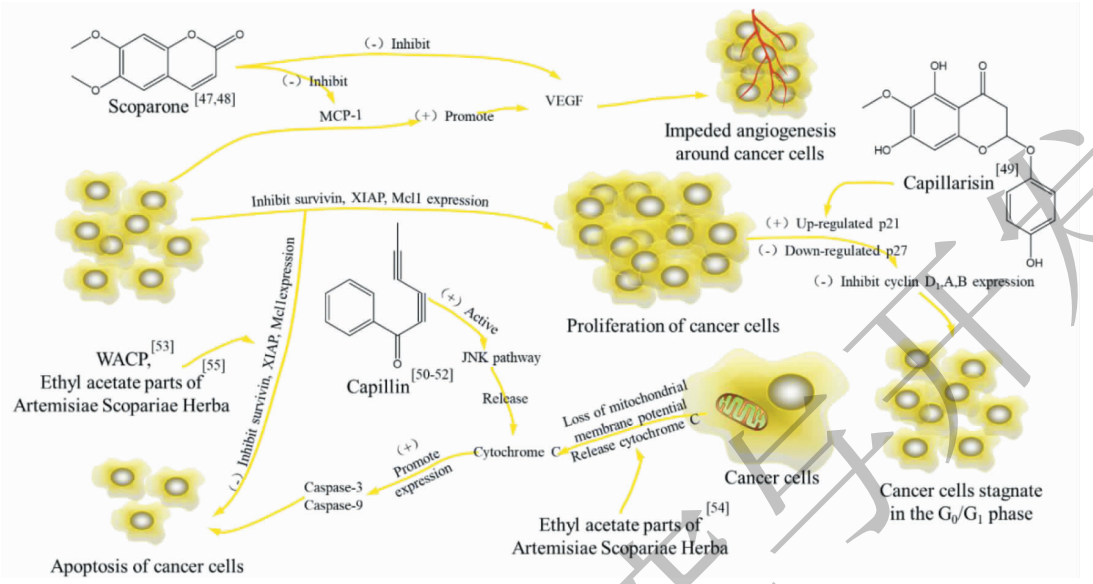

图 11　茵陈提取物及其单体组分对癌细胞/组织的调节机制

Fig. 11　Regulatory mechanism of extracts from Artemisiae Scopariae Herba and its monomer components on cancer cells/tissues

2.4　平喘作用

Cui[59]和 Lin[60]研究发现加味茵陈蒿汤通过改善体内 IL-10、IL-17 表达与 Th17/Treg 失衡,在治疗儿童湿热哮喘持续期具有较高的安全性。Liu[61]和 Lv[62]通过实验发现,6,7-二甲氧基香豆素可上调支气管哮喘豚鼠 TSMC RyR2 的表达,改善 IFN-γ、IL-4、IgE 的水平进而抑制哮喘。此外,Fang[63]和 Chi[64]还发现,6,7-二甲氧基香豆素下调哮喘豚鼠血浆中 IL-5、IL-2 和肺组织细胞溶酶体磷脂酶 A2(lysosomal phospholipase A2,PLA2)的含量,并在体外抑制豚鼠脾淋巴细胞转化,是通过免疫学途径抑制哮喘的途径之一(机制见图 12)。

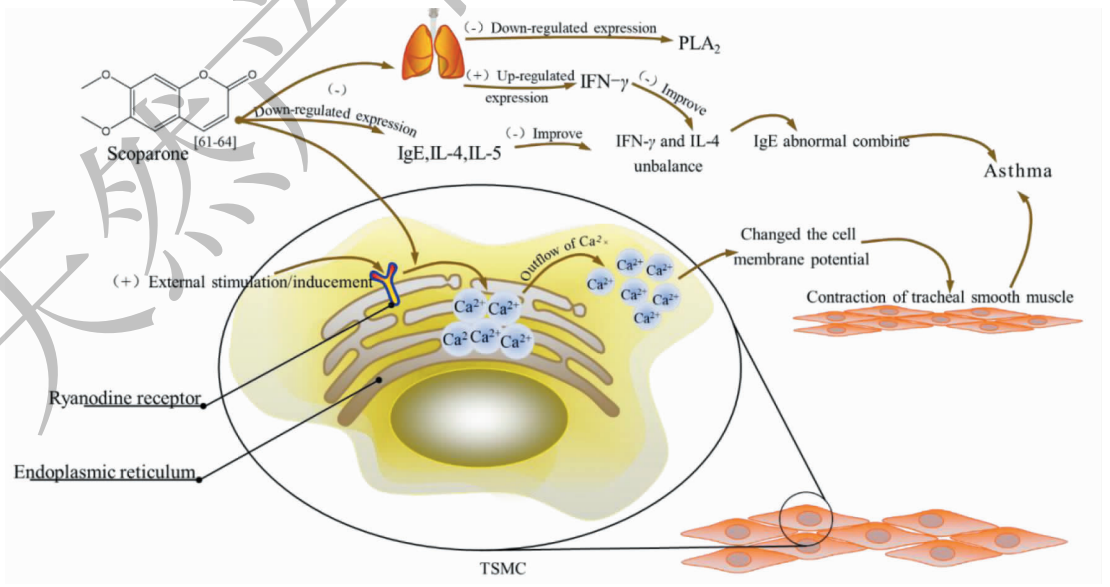

图 12　6,7-二甲氧基香豆素对哮喘豚鼠气管平滑肌细胞的调节

Fig. 12　Regulation of 6,7-dimethoxycoumarin on tracheal smooth muscle cells in guinea pigs with asthma

3 茵陈的临床应用

茵陈在临床上多以复方的应用为主，主要包括以茵陈为“君药”的茵陈蒿汤（由茵陈、大黄、栀子组成）、茵陈五苓散（由茵陈蒿、茯苓、泽泻、猪苓、桂枝、白术组成）、茵陈四逆汤（由甘草、茵陈蒿、干姜、附子组成）等。临床研究表明，茵陈复方多通过影响患者体内肝胆功能，如 ALT、AST 等水平，广泛用于肝胆疾病的治疗，如新生儿黄疸、肝炎、肝内胆汁淤积症等（表 5）。

表 5 茵陈复方在临床上的应用

Table 5 Clinical application of Yin chen Compound

序号 No.	复方名称 Compound name	病症 Disease	作用机制 Mechanism	参考文献 Reference
1	茵陈蒿汤 Yinchenhao decoction	高胆红素血症	降低血清 TSB 水平，促进黄疸消退	65
2		妊娠期肝内胆汁淤积症	降低 IFN-γ 水平，升高 IL-4 水平，维持 Th1/Th2 比值平衡	66
3			降低雌激素水平，消退妊娠期临床症状	67
4		黄疸型肝炎	降低 TSB、DBIL 与 GPT 水平	68
5		急性化脓性胆管炎	降低血清 ALT、AST、TSB 水平	69
6		慢性肝衰竭阳黄证	降低 ALT、AST、TBil、PT、LPS 和升高 Alb、PTA 及终末期肝病模型评分	70
7		慢性乙型重型肝炎	改善患者血清 ALT、AST、TBIL、PTA、NH3 水平	71
8		急性梗阻性化脓性胆管炎	降低血清 ALT、AST、TBIL、DBIL 含量	72
9		母婴 ABO 血型不合	降低孕妇血清 Ig G 抗体效价及新生儿溶血发生率	73，74
10		母婴 ABO 血型不合	降低 ABO 母婴血型不合孕妇抗体滴度，改善母体免疫功能	75
11		湿热困脾型 2 型糖尿病	改善糖尿病中医证候、症状、血糖、糖化血红蛋白	76
12	茵陈五苓散 Yinchen Wuling powder	阳黄湿重于热型黄疸	降低血清 TSB、DBIL、ALT、AST 水平	77
13		慢性乙型肝炎轻度黄疸	改善 ALT、AST、TBIL 等肝功能指标	78
14		非酒精性脂肪肝	改善 γ-GT、AST、ALP 与 ALT 等水平	79，80
15		非酒精性脂肪肝	改善 BMI、WC、FPG、FINS、TG、ALT、hs-CRP、IL-6、TNF-α、HOMA-IR 水平	81
16		肝纤维化	改善血清 ALT、AST、ALB、TBIL 等肝功能指标水平及 HA、PCIII、LN、IV-C 等肝纤维化指标水平	82
17	茵陈四逆汤 Yinchen Sini Decoction	慢性乙型肝炎阴黄	降低 ALT、AST 和 TBIL 水平	83
18	茵陈苓桂术甘汤 Yinchen Linggui Zhugan Decoction	非酒精性脂肪性肝炎	降低 AST、ALT、γ-GT、TCh 水平	84
19	皂术茵陈方 Zaozhu Yinchen Recipe	非酒精性脂肪性肝炎	改善 ALT、AST、TCh、TG 含量	85
20	茵陈丹芍汤 Yinchen Danshao Decoction	妊娠期肝内胆汁淤积症	降低血清 TBA 浓度/尿液 TBA 浓度比值	86

4 结语

综上所述，茵陈所含化学成分复杂，具有多种生物活性。近年来，国内外学者多围绕其复方及单体化合物的药理作用、生物活性及临床方面开展较为

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深入的研究,归纳如下:①茵陈及其单体化合物可调控 PI3K/Akt/NF-κB 等信号通路,影响 caspase-1、Smad3 等蛋白和 iNOS、COX-2、TNF-α 等细胞因子的表达,发挥其保肝利胆、退黄利湿、抗炎、抗病毒、抗肿瘤和神经系统等药理活性;②茵陈的临床应用多以复方为主,如古方"茵陈蒿汤"、"茵陈五苓散"、"茵陈四逆汤"等,常用于肝胆疾病的治疗。随着研究的不断深入,茵陈的药理作用和功能主治将更加明确,这对指导临床用药和新药开发是非常有必要的。但对茵陈的研究也存在以下问题:①目前茵陈的相关基础研究较薄弱,如治疗黄疸、利胆及其有效单体的相关机制和毒理研究较少;②对其主要单体及经典复方的药理活性研究还不够深入,构效关系不明确,有效成分的作用机制未能阐明,如复方多集中于肝胆疾病的治疗,对其他疾病的研究较少。因此,今后应当加强其药效学基础及其相关分子机制的系统研究,或进行复方联合治疗的详细研究,以促进茵陈单体及其复方制剂的研究开发与临床应用的推广。

参考文献

1 Wu LH, et al. Research progress on the relationship between the pharmacological action and structure-activity of simple coumarin[J]. Herald Med(医药导报), 2010, 29: 498-501.

2 Lin HC, et al. Structure-activity relationship of coumarin derivatives on xanthine oxidase-inhibiting and free radical-scavenging activities[J]. Biochem Pharmacol, 2008, 75: 1416-1425.

3 Hu RS, et al. Choleretic principles of *Artemisia scoparia*[J]. Acta Pharm Sin(药学学报), 1965, 12: 289-293.

4 Xie T, et al. Research progress of *Artemisia scoparia* and *Artemisia capillaris* on chemical constituents and pharmacological effect[J]. Strait Pharm J(海峡药学), 2004, 16(1): 8-13.

5 Okuno I, et al. Studies on choleretic constituents in *Artemisia capillaris* Thunb[J]. Chem Pharm Bull, 1988, 36: 769-775.

6 Chandrasekharan I, et al. Flavonoids from *Artemisia scoparia*[J]. Planta Med, 1981, 43: 310-311.

7 Yang CF. Fluorescent properties and analysis of scoparone and 7-methoxy coumarin in Chinese herbal medicines[D]. Shijiazhuang: Hebei Normal University(河北师范大学), 2009.

8 Wang ZW, et al. Isolation and identification of chemical constituents from *Artemisia capillaries* Thunb[J]. J Shenyang Pharm Univ(沈阳药科大学学报), 2008, 25: 781-784.

9 Muhammad SA, et al. Structural distinction between sabandins A and B from *Artemisia scoparia* Waldst. (Asteraceae)[J]. Nat Prod Res, 2014, 17(1): 1-4.

10 Chen JH, et al. Research progress of plant *O*-methoxide flavonoids and *O*-methyltransferases[J]. Nat Prod Res Dev(天然产物研究与开发), 1-19 [2021-01-25]. http://kns.cnki.net/kcms/detail/51.1335.Q.20210120.1438.006.html.

11 Zhang QW, et al. Studies on chemical constituents in buds of *Artemisia scoparia*[J]. China J Chin Mater Med(中国中药杂志), 2002, 27: 202-203.

12 Kitagawa I, et al. Capillartemisin A and B, two new choleretic principles from Artemisiae Capillaris Herba[J]. Chem Pharm Bull, 1983, 31: 352-355.

13 Xie T, et al. Acetylenes and flavonoids from *Artemisia scoparia* Ⅱ[J]. Chin J Nat Med(中国天然药物), 2005, 2(3): 86-89.

14 Namba T, et al. A flavone from *Atremisia capollaris*[J]. Phytochemistry, 1983, 22: 1057-1058.

15 Kiso Y, et al. Antihepatotoxic principles of *Artemisia capillaris buds*[J]. Planta Med, 1984, 50(1): 81-85.

16 Tan XJ, et al. Simultaneous determination of 13 bioactive comounds in Herba Artemisiae Scopariae(Yin Chen) from different harvest seasons by HPLC-DAD[J]. J Pharmaceut Biomed, 2008, 47: 847-853.

17 Lin S, et al. Studies on chemical constituents in buds of *Artemisia scoparia*(Ⅲ)[J]. China J Chin Mater Med(中国中药杂志), 2004, 29: 430-431.

18 Yen MH, et al. *Artemisia capillaris* inhibited enterovirus 71-induced cell injury by preventing viral internalization[J]. Kaohsiung J Med Sci, 2017, 34: 150-159.

19 Zhang ML. Research about antibacterial activity of extractive and effective ingeredients from *Artemisil capillaris*[D]. Yanji: Yanbian University(延边大学), 2015.

20 Zhang DZ, et al. Study on the chemical constituents of *Artemisia scoparia*[J]. J Guangdong Pharm Univ(广东药学院学报), 1997, 13: 144-145.

21 Park KM, et al. High-performance liquid chromatographic analysis for quantitation of marker compounds of *Artemisia capillaris* Thunb[J]. Arch Pharm Res, 2012, 35: 2153-2162.

22 Zhao Y, et al. UFLC/MS-IT-TOF guided isolation of anti-HBV active chlorogenic acid analogues from *Artemisia capillaris* as a traditional Chinese herb for the treatment of hepatitis[J]. J Ethnopharmacol, 2014, 156: 147-154.

23 Du Y, et al. Exploring the relationship between harvest stage of *Artemisia capillaries* Thunb and its active principle as well as pharmacology[J]. Guangming Tradit Chin Med(光明中

天然产物研究与开发

医),2012,27:2345-2346.

24 Liu JS,et al. Analysis of chemical constituents of the volatile oil of capillary wormwood herb by GC-MS[J]. Chem Anal Meter(化学分析计量),2014,23(4):17-19.

25 Zhang ZX,et al. GC-MS analysis of essential oils from *Artemisia capillaris* herba[J]. J Xianyang Norm Univ(咸阳师范学院学报),2006,21(6):25-40.

26 Harinder PS,et al. Essential oil of *Artemisia scoparia* inhibits plant growth by generating reactive oxygen species and causing oxidative damage[J]. J Chem Ecol,2009,35:154-162.

27 Harinder PS, et al. *In vitro* screening of essential oil from young and mature leaves of *Artemisia scoparia* compare to its major constituents for free radical scavenging activity[J]. Food Chem Toxicol,2010,48:1040-1044.

28 Wang YL,et al. Analysis of the volatile constituents in the dried shoots of *Artemisia capillaris* Thunb. by GC-MS,smoothing and SFA methods[J]. J Pharm Anal(药物分析杂志),2013,33(1):98-102.

29 Guo FQ,et al. Analyzing of the volatile chemical constituents in *Artemisia capillaris* herba by GC-MS and correlative chemometric resolution methods[J]. J Pharmaceut Biomed,2004,35:469-478.

30 Cha JD,et al. Chemical composition and antimicrobial activity of the essential oils of *Atremisia scoparia* and *A. capillaris*[J]. Planta Med,2005,7(1):186-190.

31 Zong Y. The therapeutic effect of dihuangyin chen decoction on ABO incompatibility pregnancy in mother and child[J]. New J Tradit Chin Med(新中医),2012,44(11):76.

32 Shang Y. Leucodin attenuates inflammatory response in macrophages and lipid accumulation in steatotic hepatocytes via P2x7 receptor pathway:a potential role in alcoholic liver disease[D]. Jilin:Yanbian University(延边大学),2019.

33 Liu X,et al. Scoparone attenuates hepatic stellate cell activation through inhibiting TGF-β/Smad signaling pathway[J]. Biomed Pharmacother,2017,93:57-61.

34 Liu YP,et al. Research progress on pharmacological effect of Artemisiae Scopariae Herba[J]. Chin Tradit Herb Drug(中草药),2019,50:2235-2241.

35 Zhang LP,et al. Research advances in pharmacological action and clinical application of active ingredients of Artemisiae Scopariae Herba[J]. Anti-Infect Pharm(抗感染药学),2014,11(1):28-31.

36 Yang CC,et al. Potential antioxidant properties and hepatoprotective effects of an aqueous extract formula derived from three Chinese medicinal herbs against CCl_4-induced liver injury in rats[J]. Int Immunopharmacol,2013,15(1):106-113.

37 Gao Q,et al. The essential oil of *Artemisia capillaris* protects against CCl_4-induced liver injury *in vivo*[J]. Rev Bras Farmacogn,2016,26:369-374.

38 Wang AQ. Recent research progress on Scopariae[J]. Guangming Tradit Chin Med(光明中医),2014,29:2207-2208.

39 Tian XH. Study on anti-inflammatory chemical constituents from *Artemisia scoparia* waldst. et. kit[D]. Beijing:Beijing University of Chemical Technology(北京化工大学),2016.

40 Kim HL,et al. Scopoletin downregulates MMP1 expression in human fibroblasts via inhibition of p38 phosphorylation[J]. Mol Cell Neurosci,2018,42:2285-2293.

41 Lu C,et al. Scoparone prevents IL-1β-induced inflammatory response in human osteoarthritis chondrocytes through the PI3K/Akt/NF-κB pathway[J]. Rev Bras Farmmacogn,2016,26:369-374.

42 Khan S,et al. Anti-hyperalgesic and anti-allodynic activities of capillarisin via suppression of inflammatory signaling in animal model[J]. J Ethnopharmacol,2014,152:478-486.

43 Khan S,et al. Molecular mechanism of capillarisin-mediated inhibition of MyD88/TIRAP inflammatory signaling in *in vitro* and *in vivo* experimental models[J]. J Ethnopharmacol,2013,145:626-637.

44 Nam SY,et al. Anti-inflammatory effects of *Artemisia scoparia* and its active constituent,3,5-dicaffeoyl-epi-quinic acid against activated mast cells[J]. Immunopharm Immunot,2018,40(1):52-58

45 Ryu KJ, et al. Therapeutic effects of *Artemisia scoparia* Waldst. et Kitaib in a murine model of atopic dermatitis[J]. Clin Exp Dermatol,2018,43:798-805.

46 Wu D. Hollow fiber cell fishing and hollow fiber liquid phase microextraction with high performance liquid chromatography for studying major antitumor components in Yinchenhao decoction[D]. Taiyuan:Shanxi Medical University(山西医科大学),2018.

47 Liu HR. Antitumor activities and mechanisms of scoparone[D]. Shenyang:China Medical University(中国医科大学),2005.

48 Jang SI, et al. Scoparone inhibits PMA-induced IL-8 and MCP-1 production through suppression of NF-κB activation in U937 cells[J]. Life Sci,2006,78:2937-2943.

49 Tsui KH,et al. The inhibitory effects of capillarisin on cell proliferation and invasion of prostate carcinoma cells[J]. Cell Proliferat,2017,51:e12429.

50 Masuda Y,et al. Capillin,a major constituent of *Artemisia capillaris* Thunb. flower essential oil, induces apoptosis through the mitochondrial pathway in human leukemia HL-60

cells[J]. Phytomedicine,2015,22:545-552.

51 Cha JD,et al. Essential oil of *Artemisia capillaris* induces apoptosisin KB Cells via Mitochondrial stressand caspase a ctivation mediated by MAPK-stimulated signaling pathway[J]. Food Sci Technol,2009,74(9):175-181.

52 Lee JH,et al. Capillarisin inhibits constitutive and inducible STAT3 activation through induction of SHP-1 and SHP-2 tyrosine phosphatases[J]. Cancer Lett,2014,345(1):140-148.

53 Feng G,et al. Antiproliferative potential of *Artemisia capillaris* polysaccharide against human nasopharyngeal carcinoma cells[J]. Carbohyd Polym,2013,92:1040-1045.

54 Yan H,et al. *Artemisia capillaris* extract AC68 induces apoptosis of hepatocellular carcinoma by blocking the PI3K/AKT pathway[J]. Biomed Pharmacother,2018,98:134-141.

55 Jung KH,et al. An ethyl acetate fraction of *Artemisia capillaris*(ACE-63) induced apoptosis and anti-angiogenesis via inhibition of PI3K/AKT signaling in hepatocellular carcinoma[J]. Phytother Res,2018,32:2034-2046.

56 Jang E,et al. Evaluation of antitumor activity of *Artemisia capillaris* extract against hepatocellular carcinoma through the inhibition of IL-6/STAT3 signaling axis[J]. Oncol Rep,2017,37:526-532.

57 Kim YS,et al. Inhibition of 7,12-dimethylbenz[a]anthracene induced mouse skin carcinogenesis by *Artemisia capillaris*[J]. Food Chem Toxicol,2008,73(1):16-20.

58 Woo SM,et al. Leukodin isolated from *Artemisia capillaris* inhibits alpha-melanocyte stimulating hormone induced melanogenesis in B16F10 melanoma cells[J]. Oncol Rep,2016,37:526-532.

59 Cui ZY. Study on Th17/Treg cell imbalance of modified Yinchenhao decoction in the treatment of chronic persistent asthma in children of damp heat[D]. Jinan:Shandong University of Chinese Medicine(山东中医药大学),2012.

60 Lin H. The clinical and experimental research of Jiawei Yinchenhao decoction in the treatment of the acute exacerbation of asthma in children(damp heat syndrome)[D]. Jinan:Shandong University of Chinese Medicine(山东中医药大学),2014.

61 Liu C. Study on the anti-asthma mechanism of scoparone[D]. Shenyang:China Medical University(中国医科大学),2004.

62 Lv GJ. Effects of litaractone on IL-4 and IFN-content in asthmatic guinea pigs[D]. Shenyang:Liaoning College of Traditional Chinese Medicine(辽宁中医学院),2004.

63 Fan Y. Inhibition effect of scoparone on inflammatory mediator of asthmatic model guinea pig[D]. Shenyang:China Medical University(中国医科大学),2004.

64 Chi TY. Effects of scoparone on the proliferation of splenic lymphocytes and IL-2 production in asthmatic guinea pigs[D]. Shenyang:China Medical University(中国医科大学),2004.

65 Li M,et al. Clinical study on the treatment of dampness-heat stagnation hyperbilirubinemia of newborn with artemisia artemisia decoction plus external washing[J]. Hebei J Tradit Chin Med(河北中医),2019,4:383-385.

66 Yang XB. Effect of *Artemisia argyi* decoction on Th1/Th2 balance in patients with intrahepatic cholestasis during pregnancy[J]. Modern J Integr Tradit Chin West Med(现代中西医结合杂志),2019,28:1885-1887.

67 Mao L. Effect of *Artemisia stelleriana* decoction on estrogen level in intrahepatic cholestasis during pregnancy[J]. J Sichuan Tradit Chin Med(四川中医),2016,34(3):94-95.

68 Xie B. Clinical effect of Yinchenhao decoction in the treatment of icteric hepatitis[J]. Chin Mod Doctor(中国现代医生),2018,56(15):108-110.

69 Chen L,et al. Clinical efficacy and prognosis of *Artemisia annua* decoction in the treatment of acute suppurative cholangitis[J]. Shanxi Tradit Chin Med(陕西中医),2017,38(1):37-38.

70 Lv JL,et al. Clinical observation of Yinchenhao decoction in the treatment of yang huang zheng with chronic liver failure[J]. Chin J Integr Tradit West Med Liver Dis(中西医结合肝病杂志),2017,27:134-136.

71 Liu XY,et al. Clinical research on Yinchenhao decoction and shengmai powder in treating chronic severe hepatitis B[J]. Guangming Tradit Chin Med(光明中医),2015,30:1878-1880.

72 Chen HG,et al. Clinical observation on the treatment of acute obstructive suppurative cholangitis in the elderly with Yinchenhaotang[J]. Guangxi J Tradit Chin Med(广西中医药大学学报),2015,18(4):17-19.

73 Song FZ. Clinical efficacy comparison of Yinzhihuang oral liquids and Yinchenhao decoctions in ABO incompatibility treatment[J]. World Clin Med(世界临床药物),2015,36:628-630.

74 Liu M,et al. Clinical observation on treatment of 126 cases of incompatibility hemolytic disease between newborn and infant with blood type by Yinchenhaotang[J]. Youjiang Med J(右江医学),2013,41:370-371.

75 Zhang M. Effect of virgate wormwood decoction on ABO blood group incompatibility titer and immune function in pregnant women[J]. World Chin Med(世界中医药),2016,11:2256-2258.

天然产物研究与开发

76 Qin CY, et al. Clinical observation of 30 cases of damp-heat type 2 diabetes mellitus with spleen entrapment treated by Yinchen artemisia decoction[J]. Diabetes New World(糖尿病新世界),2015(5):56.

77 Lian YY. The clinical effect of acupuncture combined with Yinchen Wuling powder in the treatment of yang yellow and wet heavier than heat jaundice[J]. Chin J Convalescent Med(中国疗养医学),2020,29:131-133.

78 Liang Y. Clinical observation on the treatment of mild jaundice in chronic hepatitis B with Yinchenwuling powder[D]. Nanning:Guangxi University of Traditional Chinese Medicine(广西中医药大学),2019.

79 Liu Y. Analysis of clinical value of Yinchen Wuling powder for nonalcoholic fatty liver disease[J]. Guide Chin Med(中国医药指南),2019,17(30):222-223.

80 Yang H. Clinical study of Yinchen Wuling powder in the treatment of nonalcoholic fatty liver disease[J]. Chin Foreign Med Res(中外医学研究),2015,13(5):39-40.

81 Liao ZM. Study of Yinchen Wuling in powder on insulin resistance and inflammatory markers change in patients with non-alcoholic fatty liver[D]. Guangzhou:Guangzhou University of Traditional Chinese Medicine(广州中医药大学),2013.

82 Chen B. Clinical study on the effect of Yinchen Wuling powder on liver function and serological index in patients with liver fibrosis[J]. Shandong J Tradit Chin Med(山东中医杂志),2012,31:162-164.

83 Liang Y, et al. Clinical observation of herbal medicine in treatment of patients with icteric chronic hepatitis B[J]. J Pract Hepatol(实用肝脏病杂志),2018,21:975-976.

84 Xue XX, et al. Clinical effect and mechanisms of Yinchen Linggui Zhugan decoction in treatment of non-alcoholic steatohepatitis[J]. Chin Med(中国医药),2020,15:907-911.

85 Chen SD, et al. Clinical study on the treatment of 40 cases of non-alcoholic steatohepatitis with Saponification yinchen Prescription[J]. Tradit Chin Med J(中医药通报),2015,14(1):46-48.

86 Liu F, et al. Clinical observation about treatment on intrahepatic cholestasis of pregnancy in mid trimester of pregnancy Yinchen Danshao decoction[J]. J Liaoning Univ Chin Med(辽宁中医药大学学报),2013,15(10):104-106.

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13 Zhao H, You X, Chen Q, et al. Icariin improves age-related testicular dysfunction by alleviating Sertoli cell injury via up-regulation of the ERα/Nrf2-signaling pathway[J]. Front Pharmacol,2020,11:677.

14 Rebourcet D, Wu J, Cruickshanks L, et al. Sertoli cells modulate testicular vascular network development, structure, and function to influence circulating testosterone concentrations in adult male mice[J]. Endocrinology,2016,157:2479-2488.

15 Johnson L, Thompson DL, Varner DD. Role of Sertoli cell number and function on regulation of spermatogenesis[J]. Anim Reprod Sci,2008,105(1-2):23-51.

16 Chen Q, Zhang CC, Han GF, et al. Effect of Epimedium flavonoids on decreasing secretion function of Sertoli cells in testis of natural aging rats.[J]. Chin J Pharmacol Toxicol(中国药理学与毒理学杂志),2019,33:208-215.

17 Cheng C, Mruk D. Cell junction dynamics in the testis:Sertoli-germ cell interactions and male contraceptive development[J]. Physiol Rev,2002,82:825-874.

18 Furuse M, Fujita K, Hiiragi T, et al. Claudin-1 and-2:novel integral membrane proteins localizing at tight junctions with no sequence similarity to occludin[J]. J Cell Biol,1998,141:1539-1550.

19 Susanne R, Michaela Z, Ulrich O, et al. Occludin is involved in adhesion, apoptosis, differentiation and Ca^{2+}-homeostasis of human keratinocytes:implications for tumorigenesis[J]. PLoS One,2013,8(2):e55116.

20 Qin F, Dong M, Qin Q, et al. 17-Methoxyl-7-hydroxyl-benzofuran chalcone activates Nrf2/ARE pathway to protect H9c2 cells against apoptosis[J]. Nat Prod Res Dev(天然产物研究与开发),2020,32:1038-1044.

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