柴胡属三萜皂苷成分防治肝病研究进展

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摘　要:三萜皂苷是柴胡中的一类主要的活性成分,其药理学活性一直受到研究学者的重视。迄今为止的研究发现,柴胡皂苷具有类雌激素样作用,能通过减少肝细胞损伤,抑制肝星状细胞激活和增殖进而抑制肝纤维化,以及通过抗炎、抗病毒、抗肿瘤等方式发挥肝病防治作用,且在联合治疗时能增加其他药物的肝脏靶向性和增加肝癌细胞的放射敏感性。本文综述了目前柴胡属三萜皂苷类化学成分及其防治肝病的最新研究进展,旨在为进一步探究其临床应用价值的相关性研究以及肝病新药的设计与开发提供文献依据和研究思路。

关键词:柴胡属;三萜皂苷;肝纤维化;药理作用

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Research progress on the mechanism of triterpenoid saponins from radix *Bupleuri* in treating liver diseases

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Abstract: Triterpenoid saponins are one of the main active components in radix *Bupleuri*. Their hepatoprotective effect have gained extensive attention of many researchers. It has been found that saikosaponins have estrogenic-like effects. They can protect the liver by reducing hepatocyte damage, as well as inhibit the activation and proliferation of hepatic stellate cells, and subsequently inhibit hepatic fibrosis. They have potential anti-inflammatory, anti-viral and anti-tumor effects, and they can also increase the liver targeting effect and the radiosensitivity of hepatocarcinoma cells in combination therapy. This article reviews the latest research progress on the hepatoprotective mechanism of saikosaponins, aiming to provide literature basis and research ideas for further exploring the clinical application of saikosaponins and guiding the design and development of new drugs for liver diseases.

Key words: *Bupleurum* species; triterpenoid saponin; liver fibrosis; pharmacological effect

柴胡为伞形科植物,主要分布在北半球温带、亚热带地区,全世界约有200种,而中国地区柴胡属植物约有40种,其中作为药用的有25种[1]。《中国药典》2015年版规定柴胡为北柴胡(*Bupleurum chinense* DC.)和狭叶柴胡(*Bupleurum scorzonerifolium* Willd.)的干燥根[2]。柴胡具有疏肝解郁,升举清气之功效,被历代医家用来治疗肝郁气滞症,临床疗效显著[3]。三萜皂苷类成分为其中主要的化学和生物活性成分,现有的文献表明,其具有抗炎、抗菌、抗病毒、抗氧化、肝保护等多种药理活性。国内外学者积极开展了柴胡属植物物质基础的研究,其分离得到的许多皂苷类成分在各类慢性肝病、肝纤维化、肿瘤等体内体外模型中进行了活性验证,现就近年来柴胡属三萜皂苷成分的研究进展及其防治肝病的活性机制做一综述。

1　柴胡属三萜皂苷类化学成分研究进展

柴胡属皂苷成分的结构主要为五环三萜类齐墩果烷型衍生物,近年来研究者在该属植物中分离得到了乌苏烷型和羽扇豆烷型的结构。目前柴胡中三萜皂苷的苷元主要分为12种不同结构类型,分别为13-18-环氧醚(A),异环双烯(B),12-烯-28-羧酸(C),12-烯(D),同环双烯(E),13-18-环氧醚-21-羰基(F),18-烯(G),12-烯-15-16-环氧醚(H),13-18-环氧醚-19,20-二甲基(I),12-烯-19,20-二甲基(J),15-16-环氧醚-19,20-二甲基(K),19-丙烯基(L)(图

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1),其中属于 A 型结构的皂苷为柴胡中的原生苷。柴胡皂苷糖链中一般只含葡萄糖、岩藻糖、鼠李糖和木糖等。迄今为止,已经在柴胡属植物中鉴定出 100 多种三萜皂苷,表 1 中对其中 117 个皂苷进行了结构、来源以及防治肝病相关活性的归纳。

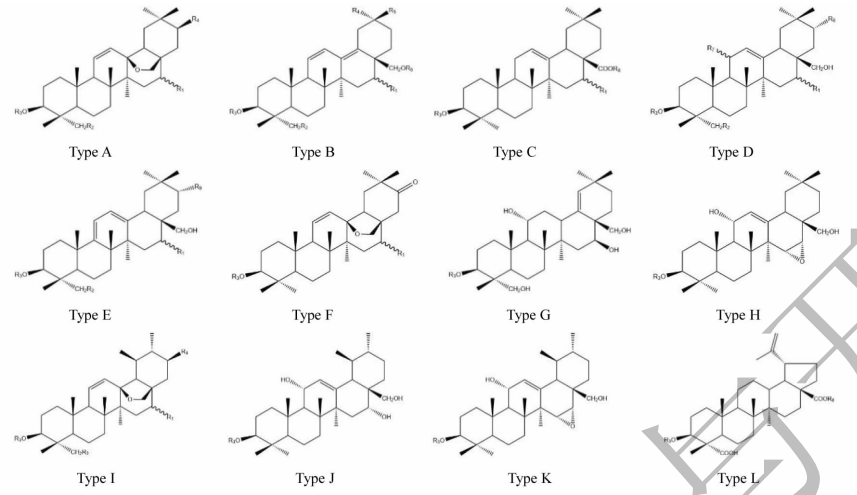

图 1　柴胡属三萜皂苷的苷元结构类型

Fig. 1　Structure type of triterpenoid saponins from radix Bupleuri

表 1　柴胡属三萜皂苷类化合物

Table 1　Triterpenoid saponins from radix Bupleuri

序号 No.	化合物名称 Compound	类型 Type	结构 Structure	来源 Source	文献 Ref	活性 Activity
1	saikosaponin a	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = β-D-glu-(1→3)-β-D-fuc	1-12	4	I[60], III[70-71], IV[73], VI[76-77], VIII[91]
2	23-*O*-acetyl-saikosaponin a	A	R_1 = β-OH, R_2 = OAc, R_4 = H, R_3 = β-D-glu-(1→3)-β-D-fuc	7	5	IX
3	2″-*O*-acetyl-saikosaponin a	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = 2″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	3,8,10	6	IX
4	3″-*O*-acetyl-saikosaponin a	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = 3″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	3,5,8,10	6	IX
5	4″-*O*-acetyl-saikosaponin a	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = 4″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	3,10	7	IX
6	6″-*O*-acetyl-saikosaponin a	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = 6″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	3,6,8,10	5	VIII[95]
7	2″,3″-diacetyl-saikosaponin a	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = 2″,3″-diacetyl-β-D-glu(1→3)-β-D-fuc	3	7	IX
8	3″,4″-diacetyl-saikosaponin a	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = 2″,3″-diacetyl-β-D-glu(1→3)-β-D-fuc	3	7	IX
9	3″,6″-diacetyl-saikosaponin a	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = 2″,3″-diacetyl-β-D-glu(1→3)-β-D-fuc	3	7	IX
10	saikosaponin c	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = β-D-glu-(1→6)-[α-L-rha-(1→4)]-β-D-glu	1-10	5	VI[76], VIII[91]

续表 1(Continued Tab. 1)

序号 No.	化合物名称 Compound	类型 Type	结构 Structure	来源 Source	文献 Ref.	活性 Activity
11	saikosaponin d	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = β-D-glu(1→3)-β-D-fuc	1,3,5,6,7,8,10	4	I[47-60], Ⅱ[67], III[67-68], IV[72], V[67-68], VI[76-77], VII[84-88], VIII[91]
12	2′′-*O*-acetyl saikosaponin d	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = 2′′-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	3,10	7	IX
13	3′′-*O*-acetyl saikosaponin d	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = 3′′-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	3,5,7,10	8	IX
14	4′′-*O*-acetyl saikosaponin d	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = 3′′-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	2,7	9	IX
15	6′′-*O*-acetyl saikosaponin d	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = 6′′-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	3,5,7,10	8	IX
16	2′′,3′′-diacetyl-saikosaponin d	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = 2′′,3′′-diacetyl-β-D-glu(1→3)-β-D-fuc	3	7	IX
17	3′′,4′′-diacetyl-saikosaponin d	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = 3′′,4′′-diacetyl-β-D-glu(1→3)-β-D-fuc	3	7	IX
18	3′′,6′′-diacetyl-saikosaponin d	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = 3′′,6′′-diacetyl-β-D-glu(1→3)-β-D-fuc	3	7	IX
19	4′′,6′′-diacetyl-saikosaponin d	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = 4′′,6′-diacetyl-β-D-glu(1→3)-β-D-fuc	3	7	IX
20	saikosaponin e	A	R_1 = β-OH, R_2 = H, R_4 = H, R_3 = β-D-glu(1→3)-β-D-fuc	7,8,10	8	VII[97]
21	3′′-*O*-acetyl saikosaponin e	A	R_1 = β-OH, R_2 = H, R_4 = H, R_3 = 3′′-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	3	7	IX
22	malonylsaikosaponin a	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = 6″-malonyl-β-D-glu-(1→3)-β-D-fuc	1,7	10	IX
23	malonylsaikosaponin d	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = 6″-malonyl-β-D-glu-(1→3)-β-D-fuc	1,7	10	IX
24	saikogenin g	A	R_1 = α-OH, R_2 = OH, R_3 = H, R_4 = H,	1,4,7	11	IX
25	saikogenin f	A	R_1 = β-OH, R 2 = OH, R_3 = H, R_4 = H,	1,4,7	12	IX
26	prosaikogenin f	A	R_1 = β-OH, R_2 = OH, R_3 = β-D-fuc, R_4 = H,	2	14	IX
27	prosaikogenin g	A	R_1 = α-OH, R_2 = OH, R_3 = β-D-fuc, R_4 = H,	9	13	IX
28	malonylbuddleja-saponin V	A	R_1 = β-OH, R_2 = OH, R_3 = 6″-$COCH_2COOH$-β-D-glu (1→2) -[β-D-glu-(1→3)]-β-D-fuc	15	15	IX
29	chikusaikoside I	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = β-D-xyl-(1→2)-β-D-glu(1→3)-β-D-fuc	6	16	IX

续表 1(Continued Tab. 1)

序号 No.	化合物名称 Compound	类型 Type	结构 Structure	来源 Source	文献 Ref.	活性 Activity
30	chikusaikoside II	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = β-D-glu(1→6)-[α-L-rha(1→4)]-β-D-glu	6	16	IX
31	16-epi-chikusaikoside I	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = β-D-xyl(1→2)-β-D-glu(1→3)-β-D-fuc	3	7	IX
32	rotundioside f	A	R_1 = α-OH, R_2 = H, R_4 = H, R_3 = β-L-rha(1→2)-β-D-glu(1→2)-β-D-fuc	14	17	III[92], VII[23]
33	rotundioside g	A	R_1 = α-OH, R_2 = H, R_4 = H, R_3 = β-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc	14	17	VII[23]
34	3-acetoxy-16α-hydroxy-13, 28-epoxy-olean-11-en-3β-yl-[β-D-glucopyrano-syl-(1→2)]-[β-D-glucopyranosyl-(1→3)]-β-D-fucopyrano side	A	R_1 = α-OH, R_2 = Oac, R_4 = H, R_3 = [β-D-glu-(1→2)]-[β-D-glu-(1→3)]-β-D-fuc	6	18	IX
35	3β, 16β, 23-trihydroxy-13, 28-epoxy-olean-11-en-3β-yl-[β-D-glucopyrano-syl-(1→2)]-[β-D-copyranosyl-(1→3)]-β-D-fucopyranoside	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = [β-D-glu-(1→2)]-[β-D-glu-(1→3)]-glu-β-D-fuc	15	19	IX
36	3-*O*-β-D-glucopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→3)]-β-D-fucopyr-anosyl-3β, 16α, 23-trihydroxy-13, 28-epoxyolean-11-ene	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = β-D-glu(1→2)-[β-D-glu(1→3)]-β-D-fuc-	12	20	IX
37	3-*O*-β-D-glucopyranosyl-(1→2)-[4-*O*-sodium sulfate-β-D-glucopyranosyl-(1→3)]-β-D-fucopyranosyl-3β, 16α, 23-trihydroxy-13, 28-epoxyolean-11-ene	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = β-D-glu(1→2)-[4-*O*-NaSO3-β-D-glu-(1→3)]-β-D-fuc-	12	20	IX
38	sandrosaponin I	A	R_1 = β-OH, R_2 = OH, R_4 = H, R_3 = 4″SO 3-β-D-glu(1→2)-[β-D-glu(1→3)]-β-D-fuc	12	21	III[22]
39	rotundioside q	A	R_1 = α-OH, R_2 = H, R_4 = α-OH, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	VII[23]
40	rotundioside s	A	R_1 = α-OH, R_2 = H, R_4 = α-OH, R_3 = β-D-rha(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	VII[23]
41	rotundioside t	A	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	VII[23]
42	3-*O*-β-D-glucopyranosyl-(1→2)-[β-D-glucopyranosyl-(1→3)]-β-D-fucopyr-anosyl-21-*O*-β-D-glucoyranosyl-3β, 16β, 21β, 23-tetrahydroxy-13, 28-epoxyolean-11-ene	A	R_1 = β-OH, R_2 = OH, R_4 = -*O*-β-D-glu(1→), R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	12	20	IX
43	saikosaponin b1	B	R_1 = α-OH, R_2 = OH, R_4 = R_5 = CH_3 R_3 = β-D-glu(1→3)-β-D-fuc	1,2,3,4,7	24	III[94]
44	saikosaponin b2	B	R_1 = β-OH, R_2 = OH, R_4 = R_5 = CH_3 R_3 = β-D-glu(1→3)-β-D-fuc	1,2,3,4,7	24	III[94], VI[76]
45	2″-*O*-acetyl-saikosaponin b2	B	R_1 = α-OH, R_2 = OH, R_4 = R_5 = CH_3 R_3 = 2″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	1,7,8,10,11	6	IX
46	3″-*O*-acetyl-saikosaponin b2	B	R_1 = α-OH, R_2 = OH, R_4 = R_5 = CH_3 R_3 = 3″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	1,7,8,10,11	6	IX
47	6″-*O*-acetyl-saikosaponin b2	B	R_1 = α-OH, R_2 = OH, R_4 = R_5 = CH_3 R_3 = 6″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	1,7,8,10,11	6	IX

续表 1(Continued Tab. 1)

序号 No.	化合物名称 Compound	类型 Type	结构 Structure	来源 Source	文献 Ref.	活性 Activity
48	saikosaponin h	B	R_1 = β-OH, R_2 = H, R_4 = R_5 = CH_3, R_6 = H R_3 = β-D-glu(1→6)-[α-L-rha-(1→4)]-β-D-glu	1,2,5,7	25	I[98]
49	saikosaponin k	B	R_1 = H, R_2 = H, R_4 = R_5 = CH_3, R_6 = H R_3 = β-D-glu-(1→2)-β-D-glu-(1→6)-[β-D-glu(1→2)]-β-D-glu	4	26	IX
50	saikosaponin l	B	R_1 = H, R_2 = H, R_4 = CH_3, R_5 = CH_2 OH, R_6 = OH R_3 = β-D-glu-(1→3)-β-D-fuc-	4	26	IX
51	saikosaponin m	B	R_1 = H, R_2 = OH, R_4 = R_5 = CH_3, R_6 = H R_3 = β-D-glu-(1→3)-β-D-fuc-	4	27	IX
52	saikosaponin n	B	R_1 = β-OH, R_2 = OH, R_4 = R_5 = CH_3, R_6 = H R_3 = β-D-glu-(1→6)-[α-L-rha-(1→4)]-β-D-glu	4	27	IX
53	saikosaponin o	B	R_1 = β-OH, R_2 = OH, R_4 = R_5 = CH_3, R_6 = H R_3 = β-D-glu(1→2)-β-D-glu(1→6)-[β-D-glu-(1→2)]-β-D-glu-	4	28	IX
54	saikosaponin p	B	R_1 = β-OH, R_2 = OH, R_4 = R_5 = CH_3, R_6 = H R_3 = β-D-glu(1→6)-[β-D-glu(1→2)-]-β-D-glu-	4	29	IX
55	saikosaponin q	B	R_1 = β-OH, R_2 = H, R_4 = R_5 = CH_3, R_6 = H R_3 = β-D-glu(1→2)-β-D-glu(1→6)-[β-D-glu(1→2)]-β-D-glu-	4	30	IX
56	saikosaponin r	B	R_1 = α-OH, R_2 = OH, R_4 = CH_2 OH, R_5 = CH_3, R_6 = H R_3 = β-D-glu-(1→2)-β-D-glu-(1→3)-β-D-fuc-	2	31	IX
57	saikosaponin s	B	R_1 = α-OH, R_2 = OH, R_4 = R_5 = CH_3, R_6 = H R_3 = β-D-glu-(1→6)-[α-L-rha-(1→4)]-β-D-glu-	2	32	IX
58	saikosaponin u	B	R_1 = α-OH, R_2 = OH, R_4 = pentito-(1→1)-β-D-glu-(6→)-COO-, R_5 = CH_3, R_6 = H R_3 = β-D-glu-(1→2)-β-D-glu-(1→3)-β-D-fuc-	2	33	IX
59	saikosaponin v	B	R_1 = α-OH, R_2 = OH, R_4 = H, R_5 = -COO-β-D-glu-CH_2-$(CHOH)_3$-CH_2OH, R_6 = H R_3 = -β-D-fuc(3-1)-β-D-glu	2	33	IX
60	saikosaponin v1	B	R_1 = α-OH, R_2 = OH, R_4 = H, R_5 = -COO-CH_2-$(CHOH)_3$-CH_2OH, R_6 = H R_3 = -β-D-fuc(3-1)-β-D-glu	1	34	IX
61	saikosaponin v2	B	R_1 = α-OH, R_2 = OH, R_4 = H, R_5 = -COO-α-D-glu-CH_2-$(CHOH)_3$-CH_2OH, R_6 = H R_3 = -β-D-fuc(3-1)-β-D-glu(2-1)-β-D-glu	1	35	IX
62	scorzoneroside a	B	R_1 = α-OH, R_2 = OH, R_3 = β-D-fuc(3-1)-β-D-glu, R_4 = $COOCH_2(CHOH)_3CH_2O$-β-D-glu, R_5 = CH_3, R_6 = H	2	36	II[99]
63	scorzoneroside b	B	R_1 = α-OH, R_2 = OH, R_3 = β-D-fuc(3-1)-β-D-glu, R_4 = $COOCH_2(CHOH)_3CH_2OH$, R_5 = CH_3, R_6 = H	2	36	II[99]

续表 1(Continued Tab. 1)

序号 No.	化合物名称 Compound	类型 Type	结构 Structure	来源 Source	文献 Ref.	活性 Activity
64	scorzoneroside c	B	R_1 = α-OH, R_2 = OH, R_3 = β-D-fuc, R_4 = COOH R_5 = CH_3, R_6 = H	2	36	II[99]
65	saikosaponin w	B	R_1 = α-OH, R_2 = H, R_4 = R_5 = CH_3, R_6 = H, R_3 = β-D-glu(1→3)-β-D-fuc-	1	37	IX
66	rotundioside e	B	R_1 = α-OH, R_2 = H, R_4 = R_5 = CH_3, R_6 = H, R_3 = β-L-rha(1→2)-β-D-glu(1→2)-β-D-fuc	3,14	38	IX
67	rotundioside v	B	R_1 = α-OH, R_2 = OH, R_4 = R_5 = CH_3, R_6 = H, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	IX
68	rotundioside w	B	R_1 = α-OH, R_2 = H, R_4 = R_5 = CH_3, R_6 = H, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	IX
69	sandrosaponin u	B	R1 = α-OH, R2 = OH, R4 = CH_3, R_5 = COO-β-D-glu-CH_2-$(CHOH)_3$-CH_2OH R3 = β-D-fuc(3-1)-β-D-glu(2-1)-β-D-glu	2	41	IX
70	3β,16α,23,28,30-pentahydroxyoleana-11,13(18)-diene 3-*O*-β-D-fucopyranoside	B	R_1 = α-OH, R_2 = OH, R_4 = CH_3, R_5 = CH_2OH, R_6 = H, R_3 = -β-D-fuc-	1	39	IX
71	sandrosapnin VI	B	R_1 = α-OH, R_2 = OH, R_4 = CH_3, R_5 = CH_2OH, R_6 = H, R_3 = β-D-glu(1→2)-[4-SO_4-β-D-glu(1→3)]-β-D-fuc-	14	22	IX
72	desulfated sandrosapnin VI	B	R_1 = α-OH, R_2 = OH, R_4 = R_5 = CH_3, R_6 = H, R_3 = β-D-glu(1→2)-[β-D-glu(1→3)]-β-D-fuc-	14	20	IX
73	rotundioside a	C	R_1 = β-OH, R_3 = SO3H, R_8 = β-D-glu-(1→6)-β-D-glu-(1→2)-β-D-glu-(1→6)-β-D-glu	14	40	IX
74	rotundioside b	C	R_1 = H, R_3 = SO3H, R_8 = β-D-glu-(1→6)-β-D-glu-(1→2)-β-D-glu-(1→6)-β-D-glu	14	40	IX
75	rotundioside c	C	R_1 = H, R_3 = SO3H, R_8 = β-D-glu-(1→6)-β-D-glu-(1→2)-β-D-glu-(1→2)-β-D-glu	14	40	IX
76	rotundioside j	C	R_1 = β-OH, R_3 = SO3H, R_8 = β-D-glu-(1→2)-β-D-glu-(1→6)-β-D-glu-(1→6)-β-D-glu	14	23	IX
77	rotundioside k	C	R_1 = β-OH, R_3 = SO_3H, R_8 = β-D-glu-(1→2)-β-D-glu-(1→6)-β-D-glu	14	23	IX
78	3-*O*-[α-L-rhamnopyranosyl(1→4)-β-D-glucopyranosyl] oleanolic acid 28-*O*-β-D-glucopyranosyl ester	C	R_1 = α-OH, R_3 = α-L-rha(1→4)-β-D-glu-, R_8 = -1-β-D-glu	13	42	IX
79	3-*O*-[α-L-rhamnopyranosyl(1→4)-β-D-glucopyranosyl] oleanolic acid 28-*O*-β-D-glucopyranosyl ester	C	R_1 = H, R_3 = α-L-rha(1→4)-β-D-glu-, R_8 = -1-β-D-glu	13	42	IX
80	saikosaponin b3	D	R_1 = β-OH, R_2 = OH, R_7 = OCH_3, R_9 = H R_3 = β-D-glu(1→3)-β-D-fuc-	1,2,5,7,8	6	II[45]
81	2″-*O*-acetyl-saikosaponin b3	D	R_1 = β-OH, R_2 = OH, R_7 = OCH_3, R_9 = H R_3 = 2″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc-	8	6	IX
82	3″-*O*-acetyl-saikosaponin b3	D	R_1 = β-OH, R_2 = OH, R_7 = OCH_3, R_9 = H R_3 = 3″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc	8	6	IX

续表 1(Continued Tab. 1)

序号 No.	化合物名称 Compound	类型 Type	结构 Structure	来源 Source	文献 Ref.	活性 Activity
83	6″-*O*-acetyl-saikosaponin b3	D	R_1 = β-OH, R_2 = OH, R_7 = OCH_3, R_9 = H R_3 = 6″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc-	8	6	IX
84	saikosaponin f	D	R_1 = β-OH, R_2 = OH, R_7 = H, R_9 = H R_3 = α-L-rha(1→4)-[β-D-glu(1→6)]-β-D-glu-	1,7	43	IX
85	11α-methoxy-saikosaponin f	D	R_1 = β-OH, R_2 = OH, R_7 = 11α-OCH_3, R_9 = H R_3 = α-L-rha(1→4)-[β-D-glu(1→6)]-β-D-glu-	5,8	6	IX
86	saikosaponin b4	D	R_1 = α-OH, R_2 = OH, R_7 = OCH_3, R_9 = H R_3 = β-D-glu(1→3)-β-D-fuc-	1,4,5,7	44	IX
87	3″-*O*-acetyl-saikosaponin b4	D	R_1 = α-OH, R_2 = OH, R_7 = OCH_3, R_9 = H R_3 = 3″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc-	5	6	IX
88	6″-*O*-acetyl-saikosaponin b4	D	R_1 = α-OH, R_2 = OH, R_7 = OCH_3, R_9 = H R_3 = 6″-*O*-acetyl-β-D-glu(1→3)-β-D-fuc-	7	5	IX
89	3″,4″-diacetyl-saikosaponin b4	D	R_1 = α-OH, R_2 = OH, R_7 = OCH_3, R_9 = H R_3 = 3″,4″-diacetyl-β-D-glu(1→3)-β-D-fuc-	3	7	IX
90	rotundioside d	D	R_1 = α-OH, R_2 = H, R_7 = H, R_9 = H R_3 = α-L-rha(1→2)-β-D-glu(1→2)-β-D-glu-	14	95	IX
91	hydroxysaikosaponin a	D	R_1 = β-OH, R_2 = OH, R_7 = OH, R_9 = H, R_3 = β-D-glu-(1→3)-β-D-fuc-	7	9	IX
92	hydroxysaikosaponin d	D	R_1 = α-OH, R_2 = H, R_7 = OH, R_9 = H, R_3 = β-D-glu-(1→3)-β-D-fuc-	7	9	IX
93	hydroxysaikosaponin c	D	R_1 = α-OH, R_2 = H, R_7 = OH, R_9 = H, R_3 = α-L-rha(1→4)-[β-D-glu-(1→6)]-β-D-glu-	7	9	IX
94	rotundioside u	D	R_1 = α-OH, R_2 = OH, R_7 = α-OCH_3, R_9 = H, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	IX
95	rotundioside x	D	R_1 = α-OH, R_2 = H, R_7 = α-OCH_3, R_9 = H, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	IX
96	rotundioside y	D	R_1 = α-OH, R_2 = H, R_7 = α-OCH_3, R_9 = H, R_3 = β-D-rha(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	IX
97	rotundioside r	D	R_1 = α-OH, R_2 = H, R_7 = α-OCH_3, R_9 = OH, R_3 = β-D-rha(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	IX
98	rotundioside p	D	R_1 = α-OH, R_2 = H, R_7 = α-OCH_3, R_9 = OH, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	IX
99	saikosaponin i	E	R_1 = β-OH, R_2 = H, R_8 = H, R_3 = α-D-glu(1→6)-[α-L-rha(1→4)]-β-D-glu-	1,5,7	11	III[93]
100	prosaikogenin h	E	R_1 = β-OH, R_2 = OH, R_8 = H, R_3 = β-D-fuc-	4	28	IX
101	rotundioside o	F	R_1 = α-OH, R_3 = β-D-rha(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	VII[23]
102	bupleuroside XIII	G	R_1 = β-D-glu(1→3)-β-D-fuc(1-)	1	45	II[45]

续表 1(Continued Tab. 1)

序号 No.	化合物名称 Compound	类型 Type	结构 Structure	来源 Source	文献 Ref.	活性 Activity
103	rotundioside l	H	R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	IX
104	rotundioside m	H	R_3 = β-D-rha(1→2)-β-D-glu(1→2)-β-D-fuc-	14	23	IX
105	rotundifolioside i	I	R_1 = α-OH, R_2 = H, R_4 = H, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	46	VII[45]
106	rotundifolioside j	I	R_1 = α-OH, R_2 = H, R_4 = H, R_3 = β-D-rha(1→2)-β-D-glu(1→2)-β-D-fuc-	14	46	VII[45]
107	rotundifolioside a	I	R_1 = α-OH, R_2 = H, R_4 = H, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-glu-	14	46	VII[45]
108	rotundifolioside h	I	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	16	VII[45]
109	rotundifolioside g	I	R_1 = α-OH, R_2 = OH, R_4 = H, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-glu-	14	16	IX
110	rotundifolioside e	I	R_1 = α-OH, R_2 = H, R_4 = OH, R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	16	IX
111	rotundifolioside f	I	R_1 = α-OH, R_2 = H, R_4 = OH, R_3 = β-D-rha(1→2)-β-D-glu(1→2)-β-D-fuc-	14	16	IX
112	rotundifolioside b	J	R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	16	IX
113	rotundifolioside c	J	R_3 = β-D-rha(1→2)-β-D-glu(1→2)-β-D-fuc-	14	16	IX
114	rotundifolioside d	K	R_3 = α-L-xyl(1→2)-β-D-glu(1→2)-β-D-fuc-	14	16	IX
115	fruticesaponin a	L	R_1 = COOH, R_2 = H, R_3 = β-D-glu(1→6)-[α-L-rha(1→4)]-β-D-glu	6	47	IX
116	fruticesaponin b	L	R_1 = COOH, R_2 = β-D-glu, R_3 = β-D-glu(4-1)-α-L-rha	6	47	III[47]
117	fruticesaponin c	L	R_1 = COOH, R_2 = β-D-glu R_3 = β-D-glu(1→6)-[α-L-rha(1→4)]-β-D-glu	6	47	IX

注:①植物来源 Source

1. 北柴胡 *Bupleurum chinense*;2. 狭叶柴胡 *B. scorzonerifolium* Willd;3. 韭叶柴胡 *B. kunmingense* Y. Li et S. L. Pan
4. 黑柴胡 *B. smithii* Wolff;5. 竹叶柴胡 *B. marginatum* Wall. ex DC. ;6. 大叶柴胡 *B. longiradiatum* Turcz
7. 三岛柴胡 *B.* falcatum;8. 丽江柴胡 *B. rockii* Wolff;9. 汶川柴胡 *B. wenchuanense* Shan et Y. Li
10. 多枝柴胡 *B. polyclonum* Y. Li et S. L. Pan;11. 银州柴胡 *B. yinchowense* Shan et Y. Li;12. *Bupleurum rigidum*. L
13. *Bupleurum lancifolium*;14. 圆叶柴胡 *B. rotundifolium* L. ;15. *Bupleurum fruticosum*

②肝病相关活性研究:I 抑制 HSC 细胞激活与增殖; II 肝细胞保护; III 抗炎症反应;IV 免疫调节;V 抗氧化;VI 抗肝病毒;VII 抗肿瘤;VIII 增加肝脏靶向性;IX 无相关活性报道

Note:Liver disease-related activities:I. Inhibiting the activation and proliferation of HSCs; II. Hepatocyte protection; III. Anti-inflammattion; IV. Immune regulation; V Antioxidation; VI. Anti-hepatoviruses; VII. Anti-tumor; VIII. Increase liver targeting effect; IX. No related activity was reported.

2　柴胡皂苷防治肝病机制的研究进展

2.1　抗肝纤维化作用

肝纤维化(hepatic fibrosis)是在病毒性肝炎、脂肪性肝炎和药物性肝损伤等大多数慢性肝病中发生的细胞外基质(ECM)的过度表达和沉积[49]。晚期肝纤维化会导致肝硬化、肝功能衰竭和门脉高压,往

往需要通过肝移植来进行治疗[50]。而许多研究表明,过度沉积的 ECM 可以在损伤停止后重建,肝脏结构恢复到接近正常,肝纤维化实则是一个可逆的阶段[51]。将中药治疗应用于遏制肝纤维化进程、逆转肝纤维化已成为治疗慢性肝病、预防肝癌的研究热点。目前柴胡皂苷抗肝纤维化的机制主要有以下方面。

2.1.1 抑制肝星状细胞的激活和增殖

肝星状细胞(hepatic stellate cells,HSC)是肝内一种具有多功能、变化不定的非实质细胞,肝脏损伤时静息期 HSC 活化为肌成纤维样细胞表型。HSC 是 ECM 的主要来源,并在肝纤维化发生发展中发挥重要作用[52,53]。

雌激素已被证实对二甲基亚硝胺(DEN)和四氯化碳(CCl_4)诱导的肝纤维化动物模型具有明显的抗纤维化作用[54,55],并且能够抑制过氧化氢诱导的原代大鼠肝星状细胞的增殖与活化[56]。但同时雌激素因各种副作用在临床上的应用受到限制,而植物雌激素对治疗肝纤维化有较好的疗效且安全性高、不良反应小,为治疗肝纤维化的药物研发提供了新的选择。Lin 等[57]的研究发现柴胡皂苷(saikosaponin,SS)d 具有类雌激素样作用。SSd 通过对雌激素受体(ER)转录激活作用,调控 MAPK 信号通路,促进 P38 蛋白磷酸化,抑制细胞因子的表达,进而抑制 HSC-T6 细胞活化。并且 SSd 能够显著上调 MMP-1 的表达,减少 TIMP-1 的表达量,从而减少 ECM 的沉积。Que 等[58]发现 SSd 能够抑制 H_2O_2 诱导的 HSC-T6 细胞的激活和增殖,并认为 SSd 的这一作用来自于对 ER-β 的调节。而 Wang 等[59]在 MCF-7 细胞中同样发现了 SSd 的弱雌激素样作用。

Chen 等[60]的实验表明 SSa 和 SSd 在抑制 HSC-T6 增殖和细胞迁移等方面均呈时间和剂量依赖性,且明显诱导细胞凋亡。此外,SSa 和 SSd 能够显著降低大鼠 HSC-T6 细胞中外基质调节激酶 1/2(ERK1/2)、血小板衍生生长因子受体 1(PDGFR1)的表达,进而下调转化生长因子-β1 受体(TGF-β1R)、α-平滑肌肌动蛋白和结缔组织生长因子。同时还降低了 HSC-T6 的 P38 和 ERK1/2 蛋白的磷酸化水平。此外,SSa 和 SSd 都可以阻断 PDGF-BB 和 TGF-β1 诱导的 HSC-T6 细胞增殖和迁移。

2.1.2 调节机体氧化应激

氧化应激在各种慢性肝病(chronic liver disease,CLD)的发病机制中发挥着重要作用,几乎所有 CLD 的临床和实验条件都检测到了氧化应激的证据[61]。HSC 在肝纤维化的发生和发展过程中更容易受到自由基的攻击,从而获得肌成纤维细胞样表型[62]。活性氧的生成在肝损伤的发生和肝纤维化的发生中起着重要作用,ROS 水平升高可刺激枯否细胞和循环炎性细胞产生促纤维化介质,直接激活 HSC,导致纤维化的发生[63]。此外,诱导人造血干细胞脂质过氧化会进一步促进 I 型前胶原的合成,加快肝纤维化进程[64]

Ge 等[65]通过长期酒精灌胃方法建立酒精性肝病大鼠模型,发现酒精性肝损害时产生大量自由基,氧化-抗氧化失衡进而导致肝脏受损。柴胡皂苷中高剂量组能够显著提高 SOD 水平,从而达到保护肝细胞的作用。GSH 是体内重要的自由基清除剂及抗氧化剂,是 GSH-PX 的底物,乙醇代谢产物乙醛能直接与 GSH 结合[66],自由基清除能力下降,造成肝损伤。实验结果表明柴胡皂苷中高剂量组能够显著上调 GSH 和 GSH-PX 的含量。

Lin 等[67]通过 CCl_4 诱导 HL-7702 细胞产生氧化应激,表现为 MDA 增加、T-SOD 活性降低。并通过 SSd 显著下调 CCl_4 诱导的 NLRP3、ASC、caspase-1、IL-1、IL-18、HMGB1 的 mRNA 和蛋白表达,认为 SSd 可以通过抑制 HL-7702 细胞系的氧化应激和 NLRP3 炎性体激活而减轻 CCl_4 诱导的急性肝细胞损伤。

Fan 等[68]采用 DEN 建立大鼠肝纤维化模型,同时采用肝细胞培养的方法研究了 SSd 对四氯化碳诱导的肝细胞氧化损伤的保护作用。结果表明,SSd 能显著降低肝脏 I 型胶原沉积和血清 ALT 水平,减轻氧化应激对肝细胞的损伤。

2.1.3 抗炎作用

炎症是激活肝星状细胞导致细胞外基质沉积作用的重要环节,因而是肝纤维化过程中的一个中心特征,抑制炎症反应是抗肝纤维化重要治疗策略之一[69]。

Wu 等[70]在 CCl_4 诱导的大鼠肝纤维化模型中,发现通过补充 SSa 可以使肝脏促炎性细胞因子 TNF-α、IL-1β 和 IL-6 均受到显著抑制,并且显著增加抗炎细胞因子 IL-10。

Zhu 等[71]的研究同样表明 SSa 具有抗炎作用,其通过调节脂多糖(LPS)刺激 RAW264.7 细胞产生的炎症介质并且抑制炎症相关通路 MAPK 和 NF-κB 通路发挥其抗炎作用。除了调控炎症相关因子之

外,在细胞水平上,SSd 能够抑制 T 细胞的活动。Wong 等[72] 的研究发现 SSd 不仅能抑制 OKT3/cd28 共刺激造成的人 T 细胞的增殖,还能抑制 PMA、PMA/Ionomycin 和 Con-A 诱导的小鼠 T 细胞活化。并且 SSd 对 PMA 诱导的 T 细胞激活的抑制作用与抑制 IKK 和 Akt 活性,下调 NF-κB 信号有关。此外,SSd 能够抑制 PMA/ ionomycin 刺激的 T 细胞的 DNA 结合活性,以及 NF-AT 和激活蛋白-1(AP-1)的核易位。这些结果表明,NF-κB、NF-AT 和 AP-1(c-Fos)信号通路参与了 SSd 诱发的 T 细胞抑制。Sun 等[73] 发现 SSa 也能有效抑制小鼠 T 细胞 IL-2、IFN 和 TNF 的产生,并且通过下调 CDK6 和 Cyclin-D3 蛋白水平,上调 P27 蛋白水平,引起活化 T 细胞 G0/G1 阻滞,线粒体膜电位明显下降,细胞色素 C 从线粒体向胞液大量释放。

2.2　抗肝病毒

病毒性肝炎是由几种不同的嗜肝病毒引起,以肝脏炎症和坏死病变为主要临床表现的一类感染性疾病[74]。我国是病毒性肝炎的高流行区,近 20 年来,死亡率一直居于我国法定传染病报告的前列[75]。

Lin 等[76] 发现柴胡皂苷(SSa,SSb_2,SSc,SSd)能够作为丙型肝炎病毒(HCV)进入细胞的抑制剂从而发挥抗病毒活性。实验中采用传染性 HCV 培养系统,检测 SS 对病毒全生命周期的影响,并评价了对各种 HCV 基因型、临床分离株和人原代肝细胞的抗病毒活性。结果表明 SS 在无细胞毒性的浓度下能有效抑制丙肝病毒的感染,且主要针对的是病毒生命周期的早期阶段。其中 SSb_2 是 HCV 早期感染最为有效的抑制剂,其作用包括中和病毒颗粒、防止病毒附着和抑制病毒进入和融合。通过可溶性病毒糖蛋白的结合实验表明,SSb_2 作用于 HCV 的 E_2 糖蛋白,诱导糖蛋白构象改变,使病毒颗粒不具有感染性。此外,SSb_2 还能抑制几种基因型菌株的感染,防止血清来源的丙肝病毒与肝癌细胞结合。

Chiang 等[77] 的研究中评估了 SSa,SSc 和 SSd 的细胞毒性和抗乙型肝炎病毒(HBV)活性。结果显示,除 SSa 和 SSd 外,HBV 转染的人肝癌细胞(2.2.15 细胞)加入 SSc 后,在培养基中乙肝 E 抗原(HBeAg)水平显著降低。SSc 还具有抑制 HBV 的 DNA 复制活性,且这种抑制作用并非来自 SSc 的细胞毒性或其对 2.2.15 细胞增殖的影响。

2.3　抗肿瘤作用

肝细胞癌(HCC)是世界范围内最常见的恶性肿瘤之一,肝癌的发病率在过去几十年里一直在上升[78]。在许多情况下,HCC 是由慢性肝炎和肝硬化发展而来的。虽然手术切除、肝移植、放疗、化疗等多种治疗策略已经出现,但患者的生存状况并没有明显改善,对机体的继发性损伤也很大[79]。中药治疗可以通过抑制肝癌细胞增殖、诱导肝癌细胞凋亡、抑制侵袭转移、逆转肝癌细胞耐药性和增强机体免疫力等作用达到控制和杀灭肝癌细胞的目的,越来越受到人们的关注。

环氧合酶-2(COX-2)是前列腺素生产中的限速酶,通常由炎症反应刺激引起,已被证明与癌变和肿瘤进展有关[80]。研究发现在早期肝细胞癌中存在 COX-2 的过表达[81]。研究表明,C / EBPβ 是至关重要的致癌物质,此外,C / EBPβ 的激活是肝细胞增殖和肝纤维化不可或缺的一步[82]。Lu 等[83] 通过 DEN 在 SD 大鼠中诱导肝细胞癌模型,并发现 SSd 的给药组与模型组相比可以显著抑制大鼠的 C/EBPβ 和 COX-2 的表达,从而遏制肝细胞癌的发生。

Hou 等[84] 观察了 SSd 对人肝癌 SMMC-7721 细胞中 COX-2 的影响,发现 SSd 在诱导肝癌 SMMC-7721 细胞增殖、诱导凋亡的同时,能够明显下调其中 COX-2 的 mRNA 及蛋白水平,降低 COX-2 活性,抑制 PGE2 的释放,且此作用可能通过调节人肝癌细胞 HIF-1α/ COX-2、STAT3/COX-2 信号通路实现[85]。

Jia 等[86] 研究发现,SSd 对人肝癌细胞 HepG2 和 Hep3B 增殖的抑制呈剂量依赖性。SSd 通过诱导人体抑癌基因 p53 表达和进一步上调 p21/WAF1 蛋白表达,在 G1 期阻断细胞周期的进展。此外,SSd 能够增加抑制因子 IkBa 在细胞质中的表达并抑制细胞核中 NF-κB 的表达和活性,随后 SSd 还会抑制抗凋亡蛋白 Bcl-XL 在 HepG2 和 Hep3B 细胞中的表达。Yang 等[87] 同样发现 SSd 作用于肝癌细胞株 HepG2 细胞时能产生显著抑制效果,促进 LC3-II 的表达以发生自噬。Chiang 等[88] 的研究表明 SSd 对 HepG2 人肝癌细胞的细胞毒性是通过激活 caspase 3 和 caspase 7 来诱导细胞凋亡。

新研究还发现,在低氧条件下,SSd 能够增加肝癌细胞的放射敏感性。缺氧环境是恶性肿瘤快速生长的一个共同特征,它会促进癌症的进展,导致对放疗和化疗的抵抗[89]。Wang 等[90] 采用皮下注射

SMMC-7721 细胞建立异种移植瘤模型,在低氧条件下,实验发现 SSd 能够剂量依赖性增加肝癌细胞的放射敏感性。通过进一步机制研究表明,SSd 能够上调 P53 基因和 Bax,同时在缺氧条件下通过抑制 HIF-1α 表达从而下调 Bcl-2。并且这些作用在 HIF-1α 抑制剂 PX-478 存在的时候被显著增强。体内数据也显示 SSd 联合放疗治疗肝癌比单一治疗更能抑制肿瘤异种移植的生长。因此,SSd 可作为肝癌放疗的潜在增敏剂。

2.4 增强药物靶向性

Feng 等[91]通过实验发现 SSa、SSc、SSd 通过调节药物转运蛋白增强药物的肝脏靶向作用。这三种 SS 对转运蛋白活性有不同程度的影响,它们都能抑制 Pgp 过表达的 HEK293 细胞中 Pgp 的活性,并且增加了 OCT2 过表达的 HEK293 细胞中 OCT2 的底物摄取。并且 SSc 和 SSd 抑制了 HEK293 细胞中多药耐药相关蛋白 MRP2 的活性以及 BRL-3A 细胞中 MRP2 的高表达。而 SSd 能够抑制 gsh 刺激的 HEK293 细胞中 MRP1 的活性。

3 总结与展望

近年来不断有研究发现柴胡属三萜皂苷成分具有多种潜在的生物活性和药理作用,不仅能通过减少肝细胞损伤,抑制肝星状细胞激活和增殖进而抑制肝纤维化,以及抗炎、抗病毒、抗肿瘤和增强免疫的方式达到防治肝病的效果,还能在联合治疗时增加其他药物的肝脏靶向性,以及增加肝癌细胞的放射敏感性。目前柴胡属中发现的 12 类三萜皂苷中 A 型皂苷的活性最为显著,推测其母核 13 和 18 位之前的环氧醚结构起了关键作用,同样具有该结构的 I 型和 J 型结构的化合物也显示了一定的活性。在目前已有的活性研究中,SSa 具有最为显著的抗炎作用,SSd 与其他皂苷相比具有最强的抗肿瘤作用,SSa 和 SSd 同属 A 型结构,且只 16 位的羟基取代不同。而 SSb_2 和 SSc 比 SSa 和 SSd 具有更好的抗病毒活性。柴胡皂苷对肝脏相关疾病的药理活性是综合且显著的,具有很好的临床应用前景。对其在肝防护方面进行更系统深入的研究,进一步阐明其药理作用及分子作用机制,对指导新药的设计与开发有着重大意义。值得注意的是,柴胡属中三萜皂苷成分具有明显的种间差异,因而对柴胡属药材的标准化和规范化尤为重要。

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