REVIEW ARTICLE

A C G publications

Rec. Nat. Prod. 19:1 (2025) 1-53

records of natural products

Scleromitrion diffusum: A Comprehensive Review of its Botany, Phytochemistry, Pharmacology and Clinical Application

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Received January 18, 2025; Revised February 11, 2025; Accepted February 12, 2025)

Abstract: *Scleromitrion diffusum* (SD) is a medicinal plant belonging to the family Rubiaceae, primarily distributed across Asia. It has a long-standing history of use in Traditional Chinese Medicine (TCM) as an antipyretic-detoxicate agent. This paper reviews studies conducted between 1979 and 2024 that encompass the phytochemistry, pharmacology, and clinical applications of SD. To date, over 259 compounds have been identified from SD, including iridoids, triterpenes, flavonoids, anthraquinones, phenolic acids, essential oils, polysaccharides, and cyclic peptides. Pharmacological investigations indicate that the compounds and extracts isolated from SD exhibit a diverse range of activities in vitro and in vivo, such as anticancer, antioxidant, anti-hepatic injury, anti-inflammatory, and anti-Alzheimer's disease. Furthermore, herbal formulations containing SD have demonstrated significant efficacy in treating various conditions, including chronic gastritis and psoriasis. In summary, this review aims to provide a comprehensive overview of the current research on SD to facilitate its further development and utilization in medicinal applications.

Keywords: *Scleromitrion diffusum*; phytochemistry; pharmacology; clinical application.

1. Introduction

Plants, a precious gift from nature, serve not only as vital food sources but also as essential contributors to drug development [1,2]. As awareness of the therapeutic potential of plants grows, phytotherapy becomes an integral part of modern medical systems [3,4]. In this context, developing

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The article was published by ACG Publications
http://www.acgpubs.org/journal/records-of-natural-products January-February 2025 EISSN:1307-6167
DOI: http://doi.org/10.25135/rnp.495.2501.3411
Available online: February 26, 2025

medicinal plant products is particularly important [5,6]. This process is often significantly influenced by local traditional medical knowledge, providing valuable insights for the exploration and utilization of medicinal plants [7-9].

China has a long-standing tradition of using herbal medicine to address health concerns, which has cultivated a rich repository of natural drug resources and substantial clinical experience [10, 11]. *Scleromitrion diffusum* (Willd.) R. J. Wang (SD) is a common herb in Traditional Chinese Medicine (TCM), known for its heat-clearing and detoxifying properties [12]. With its diverse chemical composition and pharmacological activities, SD is employed in both traditional and folk medicine to treat various diseases [13-15], drawing significant attention from researchers in phytochemical studies.

Currently, over 259 compounds have been extracted and identified from SD between 1979 and 2024. These compounds include iridoids [16], triterpenes [17], flavonoids [18], anthraquinones [19], phenolic acids [20], volatile oils [21], polysaccharides [22], cyclic peptides [23], and others [24] (Figure 1 and Figure 2). Numerous studies have demonstrated that the compounds and extracts isolated from SD exhibit a wide range of pharmacological activities *in vivo* and *in vitro*, including anticancer [25], antioxidant [26], anti-hepatic injury [27], anti-inflammatory [28], anti-Alzheimer's disease [29], and others [30]. Given this breadth of research, a comprehensive review of SD is warranted. This study aims to summarize the current knowledge on the botany, phytochemistry, pharmacology, and clinical applications of SD. The insights gathered will provide a scientific foundation for future research and explore the potential therapeutic uses of this herb.

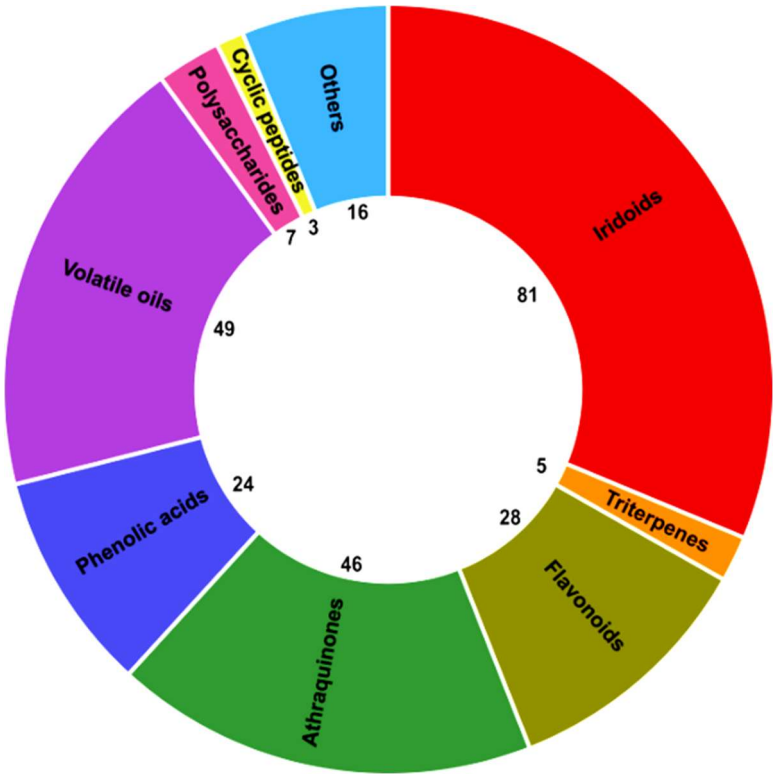

Figure 1. Distribution of the secondary metabolites among SD

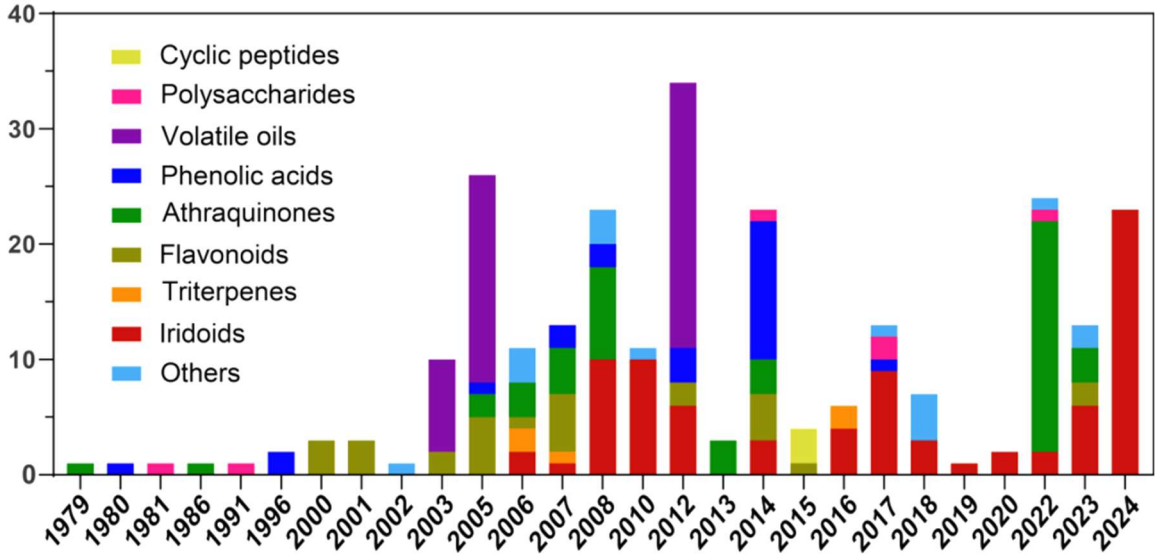

Figure 2. All secondary metabolites by source/year, n = 259

2. Search Strategy

Comprehensive research and analysis of previously published literature were conducted for studies on the botany, phytochemistry, pharmacology, and clinical application properties of SD. The search was performed using databases such as ScienceDirect, SciFinder, Medline PubMed, Google Scholar, Baidu Scholar, and CNKI by using the keywords such as *Scleromitrion diffusum*, *Hedyotis diffusa* or *Oldenlandia diffusa*. Furthermore, part of the analyzed studies was done by a manual search of articles in the reference lists of the included studies. The PRISMA template for determining the list of articles is displayed in Figure 3. The chemical structures were drawn using ChemDraw Professional 20.0 software.

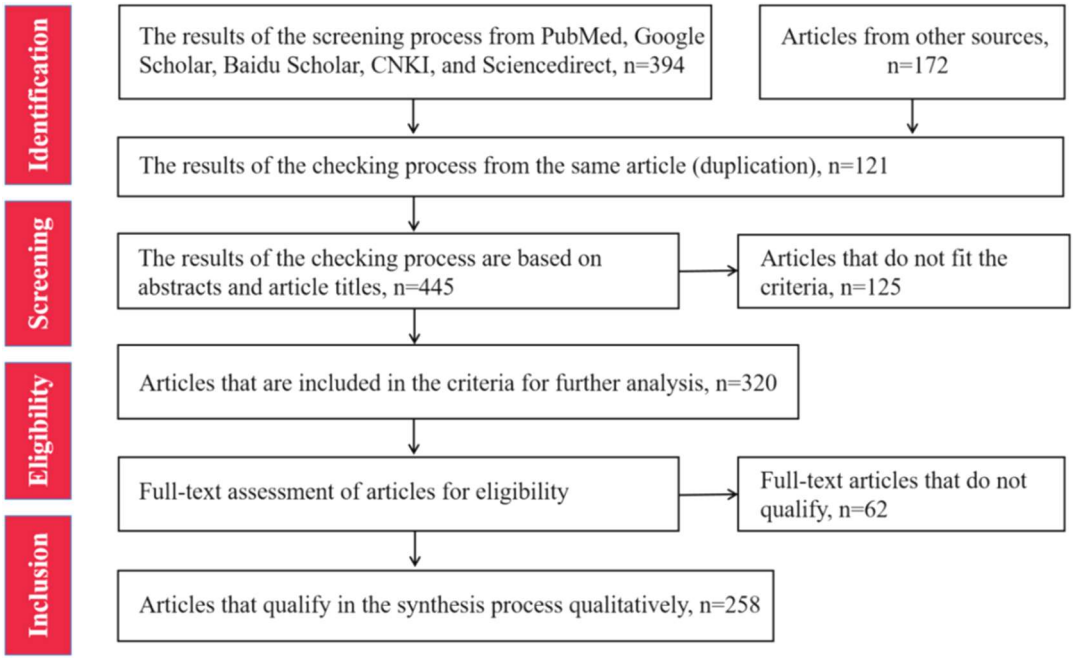

Figure 3. Research data search & selection flow.

3. Botany, Description, and Distribution

SD is a commonly used TCM known for its properties in clearing heat, detoxifying, and promoting diuresis to reduce swelling [12](Figure 4C). SD is predominantly distributed across Asia and parts of Oceania, including Assam, Bangladesh, Borneo, Cambodia, South-Central and Southeast China, the Eastern Himalayas, Hainan, India, Japan, Java, Korea, the Lesser Sunda Islands, Malaysia, Myanmar, the Nansei Islands, Nepal, the Nicobar Islands, the Philippines, Sri Lanka, Sumatra, Taiwan, Thailand, and Vietnam [16] (Figure 4D).

According to the Flora of China, SD is an annual, loose, slender, and hairless herb, reaching up to 50 cm in height (Figure 4A). The leaves are sessile, linear, 1-3 cm long, and 1-3 mm wide, with a short-tipped apex and often dry, rolled-back margins. The upper midrib is concave, and the lateral veins are not prominent. The stipules are 1-2 mm long, with a connate base and an awn-tipped apex. Flowers are solitary or paired in leaf axils, with slightly stout pedicels, 2-5 mm long, though rarely sessile or occasionally extending up to 10 mm. The calyx tube is spherical, about 1.5 mm long, and the calyx lobes are 1.5-2 mm long. The corolla is white, tubular, and 3.5-4 mm long, with a glabrous throat and corolla lobes approximately 2 mm long. The stamens are located in the throat of the corolla tube, with extended anthers. The capsule is oblate, 2-2.5 mm in diameter, and glabrous, with the top chamber splitting from the back when mature (Figure 4B) (*Scleromitrion diffusum* in Flora of China @ efloras.org, 2020).

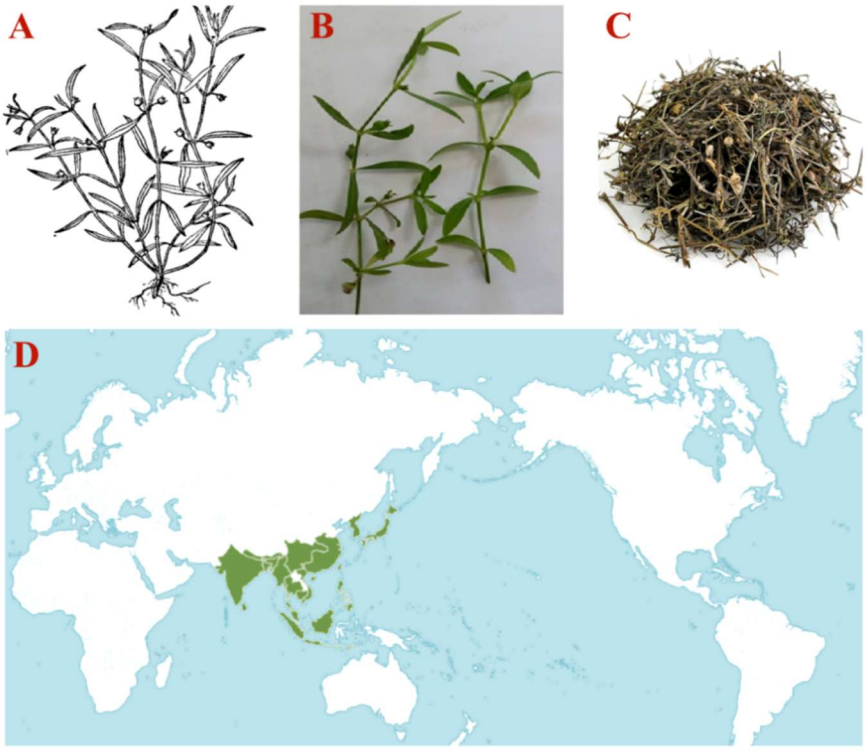

Figure 4. SD's morphology and distribution. (A) Sketch, (B) whole plant, (C) medicinal form, and (D) distribution of SD (© Copyright 2023 World Checklist of Vascular Plants).

4. Phytochemistry

To date, approximately **259** chemical constituents have been isolated from SD, with iridoids identified as the primary components. Additionally, other secondary metabolites reported from SD include triterpenes, flavonoids, anthraquinones, phenolic acids, volatile oils, polysaccharides, cyclic peptides, alkaloids, and others.

This review compiles all reported data on the phytochemical composition of SD. The reported phytoconstituents included **81** iridoids (**1**-**81**), **5** triterpenes (**82**-**86**), **28** flavonoids (**87**-**114**), **46** athraquinones (**115**-**160**), **24** phenolic acids (**161**-**184**), **49** volatile oils (**185**-**233**), **7** polysaccharides (**234**-**240**), **3** cyclic peptides (**241**-**243**), and **16** others (**244**-**259**). Each phytochemical has been numbered from (**1**-**259**) and cited in Table 1. The structures of chemical constituents have been illustrated in Figs. **5**-**11** according to the chemical classes.

Table 1. Chemical constituents reported from SD

No	Compounds	Mol. F.	Mol. Wt.	Year	Ref.
Iridoids					
1.	geniposidic acid	$C_{16}H_{22}O_{10}$	374.34	2016	[16]
2.	6-dehydro scandoside	$C_{16}H_{22}O_{10}$	374.34	2006	[17]
3.	10-*O*-acetyl geniposidic acid	$C_{18}H_{24}O_{11}$	416.38	2012	[172]
4.	10-dehydro geniposide	$C_{17}H_{22}O_{10}$	386.35	2008	[173]
5.	10-dehydro geniposidic acid	$C_{16}H_{20}O_{10}$	372.33	2006	[17]
6.	deacetyl asperulosidic acid	$C_{16}H_{22}O_{11}$	390.34	2012	[172, 174]
7.	deacetyl asperulosidic acid methyl ester	$C_{17}H_{24}O_{11}$	404.37	2008	[172, 173]
8.	6-*α*-hydro scandoside	$C_{16}H_{22}O_{11}$	390.34	2008	[175]
9.	6-*β*-hydro scandoside	$C_{16}H_{22}O_{11}$	390.34	2008	[175]
10.	6-*α*-hydro scandoside methyl ester	$C_{17}H_{24}O_{11}$	404.37	2008	[175]
11.	6-*β*-hydro scandoside methyl ester	$C_{17}H_{24}O_{11}$	404.37	2008	[175]
12.	scandoside methyl ester	$C_{17}H_{24}O_{11}$	404.37	2010	[33, 174]
13.	asperuloside acid	$C_{19}H_{26}O_{12}$	446.41	1981	[176]
14.	6-*α*-hydro-10-acetyl asperuloside acid	$C_{18}H_{24}O_{12}$	432.38	2008	[175]
15.	6-*β*-hydro-10-acetyl asperuloside acid	$C_{18}H_{24}O_{12}$	432.38	2008	[175]
16.	asperulosidic acid methyl ester	$C_{19}H_{26}O_{12}$	446.41	2010	[33]
17.	daphylloside	$C_{19}H_{26}O_{12}$	446.41	2023	[174]
18.	productasperulosidic acid butyl ester	$C_{22}H_{32}O_{12}$	488.49	2023	[174]
19.	6-*O*-methyl deacetyl asperulosidic acid methyl ester	$C_{18}H_{26}O_{11}$	418.40	2010	[33]
20.	deacetyl-6-ethoxyasperulosidic acid methyl ester	$C_{19}H_{28}O_{11}$	432.42	2010	[33]
21.	diffusoside A	$C_{19}H_{28}O_{11}$	432.42	2010	[177]
22.	diffusoside B	$C_{19}H_{28}O_{11}$	432.42	2010	[177]
23.	diffusoside C	$C_{20}H_{30}O_{12}$	462.45	2022	[178]
24.	diffusoside D	$C_{20}H_{30}O_{12}$	462.45	2022	[178]

25.	5-*O*-feruloyl scandoside methyl ester	$C_{26}H_{30}O_{14}$	566.51	2016	[16]
26.	6-*O*-methoxyl cinnamoyl scandoside	$C_{26}H_{30}O_{13}$	550.51	2016	[16]
27.	*Z*-6-O-*p*-methoxy cinnamoyl scandoside	$C_{26}H_{30}O_{13}$	550.51	2023	[174]
28.	6-*O*-*p*-hydro cinnamoyl scandoside	$C_{25}H_{28}O_{13}$	536.49	2016	[16]
29.	(*E*)-6-*O*-*p*-coumaroyl-10-*O*-formoxyl scandoside methyl ester	$C_{27}H_{30}O_{14}$	578.52	2008	[179]
30.	(*E*)-6-*O*-*p*-coumaroyl scandoside methyl ester	$C_{26}H_{30}O_{13}$	550.51	2008	[18, 172, 174, 179]
31.	(*E*)-6-*O*-*p*-coumaroyl scandoside methyl ester-10-methyl ether	$C_{27}H_{32}O_{13}$	564.54	2023	[174]
32.	(*Z*)-6-*O*-*p*-coumaroyl scandoside methyl ester	$C_{26}H_{30}O_{13}$	550.51	1991	[174, 180]
33.	(*E*)-6-*O*-*p*-coumaroyl-4'-*O*-acetyl scandoside methyl ester	$C_{28}H_{32}O_{14}$	592.55	2024	[12]
34.	(*E*)-6-*O*-*p*-coumaroyl-6'-*O*-acetyl scandoside methyl ester	$C_{28}H_{32}O_{14}$	592.55	2024	[12]
35.	(*Z*)-6-*O*-*p*-coumaroyl-6'-*O*-acetyl scandoside methyl ester	$C_{28}H_{32}O_{14}$	592.55	2024	[12]
36.	(*E*)-6-*O*-*p*-methoxy cinnamoyl scandoside methyl ester	$C_{27}H_{32}O_{13}$	564.54	2012	[18, 36, 172]
37.	(*Z*)-6-*O*-*p*-methoxy cinnamoyl scandoside methyl ester	$C_{27}H_{32}O_{13}$	564.54	2010	[36]
38.	(*E*)-6-*O*-3-hydroxy-*p*-methoxy cinnamoyl scandoside methyl ester	$C_{27}H_{32}O_{14}$	580.54	2023	[174]
39.	(*E*)-6-*O*-*p*-methoxycinnamoyl-10-*O*-acetyl scandoside acid methyl ester	$C_{29}H_{34}O_{14}$	606.58	2024	[12]
40.	(*Z*)-6-*O*-*p*-methoxycinnamoyl-10-*O*-acetyl scandoside acid methyl ester	$C_{28}H_{32}O_{14}$	592.55	2024	[12]
41.	(*E*)-6-*O*-feruloyl scandoside methyl ester	$C_{27}H_{32}O_{14}$	580.54	2012	[18, 36, 172, 174]
42.	(Z)-6-*O*-feruloyl scandoside methyl ester	$C_{27}H_{32}O_{14}$	580.54	2014	[181]
43.	*E*-6-*O*-caffeoyl scandoside methylester	$C_{26}H_{30}O_{14}$	566.51	2024	[12]
44.	diffusadoid A	$C_{44}H_{62}O_{14}$	814.97	2024	[123]
45.	diffusadoid B	$C_{44}H_{62}O_{14}$	814.97	2024	[123]
46.	diffusadoid C	$C_{44}H_{59}O_{14}$	811.94	2024	[123]
47.	diffusadoid D	$C_{44}H_{60}O_{14}$	812.95	2024	[123]
48.	diffusadoid E	$C_{42}H_{60}O_{14}$	788.93	2024	[123]
49.	diffusadoid F	$C_{42}H_{60}O_{14}$	788.93	2024	[123]
50.	diffusadoid G	$C_{44}H_{64}O_{14}$	816.98	2024	[123]
51.	diffusadoid H	$C_{44}H_{57}O_{14}$	809.93	2024	[123]
52.	diffusadoid I	$C_{28}H_{32}O_{14}$	592.55	2024	[123]
53.	diffusadoid J	$C_{30}H_{34}O_{15}$	634.59	2024	[123]
54.	diffusadoid K	$C_{30}H_{34}O_{15}$	634.59	2024	[123]
55.	diffusadoid L	$C_{28}H_{32}O_{14}$	592.55	2024	[123]

56.	diffusadoid M	$C_{30}H_{34}O_{15}$	634.59	2024	[123]
57.	diffusadoid N	$C_{30}H_{34}O_{15}$	634.59	2024	[123]
58.	diffusadoid O	$C_{29}H_{34}O_{15}$	622.58	2024	[123]
59.	diffusadoid P	$C_{31}H_{36}O_{16}$	644.61	2024	[123]
60.	11-methoxyviburtinal	$C_{10}H_8O_3$	176.17	2017	[32]
61.	monotropein methyl ester	$C_{17}H_{24}O_{11}$	404.37	2010	[33]
62.	hehycoryside C	$C_{23}H_{26}O_{11}$	478.45	2014	[182]
63.	10-*O*-benzoyl scandoside methyl ester	$C_{24}H_{28}O_{12}$	508.48	2023	[174]
64.	10-*O*-benzoyl-6'-*O*-α-L-arabino(1→6)-*β*-D-glucopyranosylgeniposidic acid	$C_{28}H_{34}O_{15}$	610.57	2010	[33]
65.	oldenlandoside III	$C_{34}H_{44}O_{20}$	772.71	2014	[182]
66.	patrinoside	$C_{21}H_{34}O_{11}$	462.49	2017	[32]
67.	suspensolide F	$C_{21}H_{34}O_{12}$	478.49	2017	[32]
68.	hedyoiridoidside A	$C_{21}H_{32}O_{10}$	444.48	2018	[60]
69.	hedyoiridoidside B	$C_{22}H_{38}O_{13}$	510.53	2018	[60]
70.	15-demethylisoplumieride	$C_{20}H_{26}O_{11}$	442.42	2017	[32]
71.	shecaoiridoidside B	$C_{21}H_{32}O_{13}$	492.47	2017	[32]
72.	jatamanin E	$C_{10}H_{14}O_5$	214.22	2017	[32]
73.	shecaoiridoidside A	$C_{22}H_{32}O_{12}$	488.49	2017	[32]
74.	kanokoside A	$C_{22}H_{34}O_{12}$	490.50	2017	[32]
75.	hedyoiridoidside C	$C_{22}H_{36}O_{10}$	460.52	2018	[60]
76.	alpigenoside	$C_{18}H_{28}O_{10}$	436.41	2012	[172]
77.	4-epiborreriagenin	$C_{11}H_{16}O_4$	212.25	2010	[33]
78.	shecaoiridoidside C	$C_{23}H_{28}O_{10}$	464.47	2017	[32]
79.	asperuloside	$C_{18}H_{22}O_{11}$	414.36	2007	[179, 183]
80.	deacetyl asperuloside	$C_{16}H_{20}O_{10}$	372.33	2012	[172]
81.	diffusadoid Q	$C_{20}H_{24}O_{12}$	456.40	2024	[123]
Triterpenes					
82.	lupenylacetate	$C_{32}H_{52}O_2$	468.77	2007	[34]
83.	arborinone	$C_{30}H_{48}O$	424.71	2016	[16]
84.	isoarborinol	$C_{30}H_{50}O$	426.73	2016	[16]
85.	oleanolic acid	$C_{30}H_{48}O_3$	456.71	2006	[17]
86.	ursolic acid	$C_{30}H_{48}O_3$	456.71	2006	[17]
Flavonoids					
87.	amentoflavone	$C_{30}H_{18}O_{10}$	538.46	2005	[36, 37]
88.	chrysin-6-*O*-glucosyl-8-*O*-arabinosyl	$C_{26}H_{28}O_{13}$	548.50	2014	[182]
89.	chrysin-6-*O*-arabinosyl-8-*O*-glucosyl	$C_{26}H_{28}O_{13}$	548.50	2014	[182]
90.	oroxylin A-*O*-glucuronic acid	$C_{22}H_{20}O_{11}$	460.39	2014	[182]
91.	wogonin-*O*-glucuronic acid	$C_{22}H_{20}O_{11}$	460.39	2014	[182]
92.	5,7-dihydroxy-3-methoxy flavonol	$C_{16}H_{12}O_6$	300.27	2007	[183]
93.	5,7,4'-trihydroxy flavonol	$C_{15}H_{10}O_6$	286.24	2007	[183]
94.	5-hydroxy-6,7,3',4'-tetramethoxy flavone	$C_{19}H_{18}O_7$	358.35	2007	[34]
95.	quercetin	$C_{15}H_{10}O_7$	302.24	2006	[17, 20, 173]
96.	rutin	$C_{28}H_{32}O_{15}$	608.55	2007	[18, 172, 184]

97.	quercetin-3-*O*-*β*-D-glucopyranside	$C_{21}H_{20}O_{12}$	464.38	2000	[18, 185, 186]
98.	quercetin-3-*O*-*β*-D-galactopyranoside	$C_{21}H_{20}O_{12}$	464.38	2005	[185]
99.	quercetin-3-*O*-(2-*O*-glucopyranosyl)-*β*-D-glucopyranside	$C_{27}H_{30}O_{17}$	626.52	2000	[18, 172, 185, 186]
100.	quercetin-3-*O*-(2-*O*-glucopyranosyl)-*β*-D-galactopyranoside	$C_{27}H_{30}O_{17}$	626.52	2001	[187, 188]
101.	quercetin-3-*O*-sambubioside	$C_{26}H_{28}O_{16}$	596.49	2012	[18, 172]
102.	quercetin-3-*O*-[2-*O*-(6-*O*-*E*-ferloyl)-*β*-D-glucopyranosyl]-β-D-galactopyranoside	$C_{37}H_{38}O_{20}$	802.69	2001	[187, 188]
103.	quercetin-3-*O*-[2-*O*-(6-*O*-*E*-feruloyl)-*β*-D-glucopyranosyl]-*β*-D-glucopyanoside	$C_{37}H_{38}O_{20}$	802.69	2003	[18, 172, 187]
104.	quercetin-3-*O*-[2-*O*-(6-*O*-*E*-sinapoyl)-*β*-D-glucopyranosyl]-*β*-D-glucopyanoside	$C_{38}H_{40}O_{21}$	832.72	2012	[172]
105.	quercetin-3-*O*-[2-*O*-(6-*O*-*E*-sinapoyl)-*β*-D-glucopyranosyl]-*β*-D-galactopyranoside	$C_{38}H_{40}O_{21}$	832.72	2015	[18]
106.	kaempferol	$C_{15}H_{10}O_6$	286.24	2003	[173, 189]
107.	kaempferol-3-*O*-*β*-D-glucopyranside	$C_{21}H_{20}O_{11}$	448.38	2005	[185]
108.	kaempferol-3-*O*-*β*-D-galactopyranoside	$C_{21}H_{20}O_{11}$	448.38	2005	[185]
109.	kaempferol-3-*O*-(2-*O*-*β*-D-glucopyranosyl)-*β*-D-galactopyranoside	$C_{27}H_{30}O_{16}$	610.52	2001	[18, 187, 188]
110.	kaempferol-3-*O*-(6-*O*-*α*-L-rhamnosyl)-*β*-D-glucopyranside	$C_{27}H_{30}O_{15}$	594.52	2005	[185]
111.	kaempferol-3-*O*-[2-*O*-(*E*-6-*O*-feruloyl)-*β*-D-glucopyranosyl]-*β*-D-glucopyranosyl	$C_{37}H_{38}O_{19}$	786.69	2000	[18, 186, 187]
112.	kaempferol-3-*O*-[2-*O*-(*E*-6-*O*-feruloyl)-*β*-D-glucopyranosyl]-*β*-D-galactopyranoside	$C_{37}H_{38}O_{19}$	786.69	2007	[34, 188]
113.	(+) dihydroquercetin	$C_{15}H_{12}O_6$	288.26	2023	[24]
114.	(+) aromadendrin	$C_{15}H_{12}O_5$	272.26	2023	[24]
Athraquinones					
115.	1,3-dihydroxy-2-methyl anthraquinone	$C_{15}H_{10}O_4$	254.24	2008	[190]
116.	1,7- dihydroxy-6-methoxy-2-methyl anthraquinone	$C_{16}H_{12}O_5$	284.27	2008	[190]
117.	1-hydroxy-2-methoxy-3-methyl-9,10-anthraquinone	$C_{16}H_{12}O_4$	268.27	2022	[19]
118.	1-hydroxy-4-methoxy anthraquinone	$C_{15}H_{10}O_4$	254.24	2013	[191]
119.	2-hydroxymethyl-1-hydroxy anthraquinone	$C_{15}H_{10}O_4$	254.24	2013	[191]
120.	robustaquinone B	$C_{17}H_{14}O_5$	298.29	2022	[19]
121.	physcion	$C_{16}H_{12}O_5$	284.27	2022	[19]
122.	erythroglaucin	$C_{16}H_{12}O_6$	300.27	2022	[19]
123.	2-hydroxy-1,3-dimethoxy anthraquinone	$C_{16}H_{12}O_5$	284.27	2005	[37]
124.	2-hydroxy-3-methyl-1-methoxy anthraquinone	$C_{16}H_{12}O_4$	268.27	2007	[192]

125.	2-hydroxy-3-methyl-4-methoxy anthraquinone	$C_{16}H_{12}O_4$	268.27	2014	[193]
126.	2-hydroxy-7-methyl-3-methoxy anthraquinone	$C_{16}H_{12}O_4$	268.27	2007	[192]
127.	2-hydroxy-1-methoxy-3-methyl anthraquinone	$C_{17}H_{14}O_5$	298.29	2007	[184]
128.	2-hydroxy-3-methyl anthraquinone	$C_{15}H_{10}O_3$	238.24	2008 2014	[173, 181]
129.	2-hydroxy-1-methoxy anthraquinone	$C_{15}H_{10}O_4$	254.24	2014 2005	[37, 181]
130.	2-hydroxy-4-methoxy anthraquinone	$C_{15}H_{10}O_4$	254.24	2008	[194]
131.	2-hydroxy-6-methyl anthraquinone	$C_{15}H_{10}O_3$	238.24	2008	[195]
132.	2-hydroxy-3-methoxy-6-methyl anthraquinone	$C_{16}H_{12}O_4$	268.27	2008	[195]
133.	2-hydroxy-3-hydroxymethyl-9,10-anthraquinone	$C_{15}H_{10}O_4$	254.24	2022	[19]
134.	2-hydroxy-6-hydroxymethyl anthraquinone	$C_{15}H_{10}O_4$	254.24	2022	[19]
135.	2-hydroxy-7-hydroxymethyl -3-methoxy anthraquinone	$C_{16}H_{12}O_5$	284.27	2008	[196]
136.	2,6-dihydroxy-3-methyl-9,10-anthraquinone	$C_{15}H_{10}O_4$	254.24	2022	[19]
137.	2,6-dihydroxy-3-methyl-4-methoxy anthraquinone	$C_{16}H_{12}O_5$	284.27	2006	[197]
138.	2,6-dihydroxy-1-methoxy-3-methyl anthraquinone	$C_{16}H_{12}O_5$	284.27	2007	[184]
139.	2,7-dihydroxy-3-methyl anthraquinone	$C_{15}H_{10}O_4$	254.24	2008	[198]
140.	3-hydroxy-2-methyl anthraquinone	$C_{15}H_{10}O_3$	238.24	2006	[17]
141.	3-hydroxy-2-hydroxymethyl anthraquinone	$C_{15}H_{10}O_4$	254.24	2023	[24]
142.	rubiadin-1-methyl ether	$C_{16}H_{12}O_4$	268.27	2023	[24]
143.	3-hydroxy-2-methyl-4-methoxy anthraquinone	$C_{16}H_{12}O_4$	268.27	1979	[199]
144.	3-hydroxy-2-methoxy-6-methyl-9,10-anthraquinone	$C_{16}H_{12}O_4$	268.27	2022	[19]
145.	3-hydroxy-2-methoxy-6-hydroxymethyl-9,10-anthraquinone	$C_{16}H_{12}O_5$	284.27	2022	[19]
146.	tectoquinone	$C_{15}H_{10}O_2$	224.26	2022	[19]
147.	2-methyl-3-methoxy anthraquinone	$C_{16}H_{12}O_4$	252.27	2006	[17]
148.	2-methoxy anthraquinone	$C_{15}H_{10}O_3$	238.24	2023	[24]
149.	2-methoxy-3-methyl-9,10-anthraquinone	$C_{16}H_{12}O_3$	252.27	2022	[19]
150.	2,3-dimethoxy-6-methyl anthraquinone	$C_{17}H_{14}O_4$	282.30	1986	[200]
151.	2-formyl-9,10-anthraquinone	$C_{16}H_{10}O_3$	250.25	2022	[19]
152.	2-hydroxymethyl anthraquinone	$C_{15}H_{10}O_3$	238.24	2013	[191]
153.	capitellataquinone D	$C_{21}H_{18}O_4$	334.37	2022	[19]
154.	diffusaquinone A	$C_{20}H_{16}O_3$	304.35	2022	[19]
155.	diffusaquinone B	$C_{21}H_{20}O_4$	336.39	2022	[19]

156.	diffusaquinone C	$C_{21}H_{20}O_5$	352.39	2022	[19]
157.	diffusaquinone D	$C_{20}H_{16}O_3$	304.35	2022	[19]
158.	diffusaquinone E	$C_{20}H_{16}O_4$	320.34	2022	[19]
159.	diffusaquinone F	$C_{20}H_{16}O_5$	336.34	2022	[19]
160.	diffusaquinone G	$C_{20}H_{16}O_5$	336.34	2022	[19]
Phenolic acids					
161.	3,4-dihydroxy benzoic acid	$C_7H_6O_4$	154.12	2007	[34]
162.	4-hydroxy-3-methoxy benzoic acid	$C_8H_8O_4$	168.15	2012	[20]
163.	4-hydroxy benzoic acid	$C_7H_6O_3$	138.12	2012	[20]
164.	4-hydroxy-3,5-dimethoxy benzoic acid	$C_9H_{10}O_5$	198.17	2012	[20]
165.	*p*-coumaric acid	$C_9H_8O_3$	164.16	2005	[17, 37]
166.	*p*-coumaric acid-*O*-glucopyranside	$C_{15}H_{18}O_8$	326.30	2014	[182]
167.	caffeic acid	$C_9H_8O_4$	180.16	2007	[34]
168.	caffeoyl hexoside	$C_{15}H_{18}O_9$	342.30	2014	[182]
169.	ferulic acid	$C_{10}H_{10}O_4$	194.19	2008	[190]
170.	ferulic acid hexoside	$C_{16}H_{20}O_9$	356.33	2014	[182]
171.	*p*-methoxy cinnamic acid	$C_{10}H_{10}O_3$	178.19	1996	[40]
172.	methoxy-cinnamoyl hexoside	$C_{16}H_{20}O_8$	340.33	2017	[201]
173.	octadecyl (*E*)-*p*-coumarate	$C_{27}H_{44}O_3$	416.33	2008	[202]
174.	3-caffeoyl quinic acid	$C_{16}H_{18}O_9$	354.31	2014	[182]
175.	4-caffeoyl quinic acid	$C_{16}H_{18}O_9$	354.31	2014	[182]
176.	5-caffeoyl quinic acid	$C_{16}H_{18}O_9$	354.31	2014	[182]
177.	3-*p*-coumaroyl quinic acid	$C_{16}H_{18}O_8$	338.31	2014	[182]
178.	4-*p*-coumaroyl quinic acid	$C_{16}H_{18}O_8$	338.31	2014	[182]
179.	5-*p*-coumaroyl quinic acid	$C_{16}H_{18}O_8$	338.31	2014	[182]
180.	3-feruloyl quinic acid	$C_{17}H_{20}O_9$	368.34	2014	[182]
181.	4-feruloyl quinic acid	$C_{17}H_{20}O_9$	368.34	2014	[182]
182.	5-feruloyl quinic acid	$C_{17}H_{20}O_9$	368.34	2014	[182]
183.	4,4'-dihydroxy-α-truxillic acid	$C_{18}H_{16}O_6$	328.32	1996	[40]
184.	4,4'-dimethoxyl-α-truxillic acid	$C_{20}H_{20}O_6$	356.37	1980	[41]
Volatile oils					
185.	6,10,14-trimethyl-2-pentadecanone	$C_{18}H_{36}O$	268.49	2005	[21]
186.	phytol	$C_{20}H_{40}O$	296.54	2005	[21]
187.	*α*-cedrol	$C_{15}H_{26}O$	222.37	2005	[21]
188.	tetradecanoic acid	$C_{20}H_{31}NO_4$	349.47	2005	[21]
189.	hexadecanoic acid methyl ester	$C_{17}H_{34}O_2$	270.46	2005	[21]
190.	hexadecanoic acid	$C_{16}H_{32}O_2$	256.46	2005	[21]
191.	1,2-benzenedicarboxylic acid isobutyl ester	$C_{11}H_{12}O_4$	208.21	2005	[21]
192.	1,2-benzenedicarboxylic acid *bis*(2-methylpropyl)ester	$C_{14}H_{18}O_4$	250.29	2005	[21]
193.	9,12,15-octadecatrienoic acid methyl ester	$C_{19}H_{32}O_2$	292.46	2005	[21]
194.	9-octadecenoic acid	$C_{18}H_{34}O_2$	282.47	2005	[21]
195.	9,12-octadecenoic acid	$C_{19}H_{34}O_2$	294.48	2005	[21]

196.	ethyl linoleate	$C_{20}H_{36}O_2$	308.51	2005	[21]
197.	triethyl phosphate	$C_6H_{15}O_4P$	182.16	2005	[21]
198.	4-vinyl phenol	C_8H_8O	120.15	2005	[21]
199.	2-methoxy-4-vinylphenol	$C_9H_{10}O_2$	150.18	2005	[21]
200.	*n*-pentadecanoic acid	$C_{15}H_{30}O_2$	242.40	2005	[21]
201.	heneicosane	$C_{25}H_{52}$	352.69	2005	[21]
202.	2,6,10,14,18,22-tetracosahexaene	$C_{24}H_{38}$	326.57	2005	[21]
203.	*α*-terpineol	$C_{10}H_{18}O$	154.25	2003	[203]
204.	geranyl acetate	$C_{12}H_{20}O_2$	196.29	2003	[203]
205.	*β*-ionone	$C_{13}H_{20}O$	192.30	2003	[203]
206.	lauric acid	$C_{12}H_{24}O_2$	200.32	2003	[203]
207.	myristic acid	$C_{14}H_{28}O_2$	228.38	2003	[203]
208.	palmitic acid	$C_{16}H_{32}O_2$	256.43	2003	[203]
209.	linoleic acid	$C_{18}H_{32}O_2$	280.45	2003	[203]
210.	*β*-linalool	$C_{10}H_{18}O$	154.25	2003	[203]
211.	isoborneol	$C_{10}H_{18}O$	154.25	2012	[204]
212.	3-(2-propenyl)-cyclohexene	C_9H_{10}	118.18	2012	[204]
213.	2-pentyl-furan	$C_9H_{14}O$	138.21	2012	[204]
214.	*cis*-2-(2-pentenyl)-furan	$C_9H_{12}O$	136.19	2012	[204]
215.	limonene	$C_{10}H_{16}$	136.24	2012	[204]
216.	3,7-dimethyl-1,6-octadien-3-ol	$C_{10}H_{18}O$	154.25	2012	[204]
217.	*D*-menthol	$C_{10}H_{20}O$	156.27	2012	[204]
218.	(-)-borneol pentanoate	$C_{10}H_{14}O_2$	166.22	2012	[204]
219.	*p*-menth-1-en-8-ol	$C_{10}H_{18}O$	154.25	2012	[204]
220.	pulegone	$C_{10}H_{16}O$	154.25	2012	[204]
221.	irisone	$C_{13}H_{20}O$	192.30	2012	[204]
222.	hexadecanal	$C_{16}H_{32}O$	240.43	2012	[204]
223.	2,6,10,14-tetramethyl-hexadecane	$C_{20}H_{42}$	282.56	2012	[204]
224.	(*Z,Z*)-9,12-octadecadienoic acid	$C_{18}H_{32}O_2$	280.45	2012	[204]
225.	(*Z*)-9,17-octadecadienal	$C_{18}H_{32}O$	264.45	2012	[204]
226.	7,10,13-hexadecatrienal	$C_{16}H_{26}O$	234.38	2012	[204]
227.	oleic acid	$C_{18}H_{34}O_2$	282.47	2012	[204]
228.	hexaldehyde	$C_6H_{12}O$	100.16	2012	[204]
229.	borneol	$C_{10}H_{18}O$	154.25	2012	[204]
230.	docosane	$C_{27}H_{56}$	380.75	2012	[204]
231.	tetracosane	$C_{22}H_{46}$	310.61	2012	[204]
232.	hexacosane	$C_{24}H_{50}$	338.66	2012	[204]
233.	heptacosane	$C_{26}H_{54}$	366.72	2012	[204]
Polysaccharides					
234.	OPD-1	-	-	2014	[43]
235.	HD-PS-1	-	-	2020	[22]
236.	HD-PS-2	-	-	2020	[22]
237.	HDW	-	-	2017	[205]
238.	HDP1	-	-	2017	[95]

239.	HDP2	-	-	2019	[44, 45]
240.	HDP3	-	-	2022	[46]
Cyclic peptides					
241.	CD1	-	-	2015	[23]
242.	CD2	-	-	2015	[23]
243.	CD3	-	-	2015	[23]
Other compounds					
244.	10(*S*)-hydroxy pheophytin	$C_{55}H_{82}N_4O_6$	895.28	2010	[206]
245.	aurantiamide acetate	$C_{27}H_{28}N_2O_4$	444.53	2008	[202]
246.	shecaocerenoside A	$C_{48}H_{93}NO_9$	828.27	2017	[32]
247.	hedyocerenoside F	$C_{46}H_{89}NO_9$	800.22	2018	[60]
248.	hedyocerenoside G	$C_{40}H_{77}NO_9$	716.05	2018	[60]
249.	hedyoceramide A	$C_{31}H_{61}NO_5$	527.83	2018	[60]
250.	hedyoceramide B	$C_{37}H_{71}NO_4$	593.98	2018	[60]
251.	9-*O*-(*trans*-*p*-coumaroyl)-alternariol	$C_{24}H_{18}O_6$	402.40	2023	[24]
252.	9-*O*-(*trans*-caffeoyl)-alternariol	$C_{24}H_{18}O_7$	418.40	2023	[24]
253.	daucosterol	$C_{29}H_{50}O$	414.72	2006	[17]
254.	*β*-sitosterol	$C_{34}H_{58}O_6$	562.83	2006	[17]
255.	stigmasterol	$C_{29}H_{48}O_2$	428.70	2006	[17, 173]
256.	stigmasterol-5,2-diene-3*β*, 7*α*-glycol	$C_{29}H_{46}O$	410.69	2002	[207]
257.	7-hydroxy-6-methoxy-coumarin	$C_9H_6O_4$	178.14	2008	[173]
258.	esculetin	$C_{10}H_8O_4$	192.17	2008	[202]
259.	4,7-dimethoxy-5-methyl-1,3-benzodioxole	$C_{10}H_{12}O_4$	196.20	2022	[19]

Note: Mol. F.: molecular formula; Mol. Wt.: molecular weight

4.1. Iridoids and Triterpenoids

Terpenoids are compounds derived from mevalonic acid (MVA) with the general formula $(C_5H_8)_n$. Among them, iridoids are monoterpenes formed by cyclization of two MVA units [31]. To date, 81 iridoids (**1–81**) have been isolated from SD, most of which having a bicyclic system consisting of oxygenated six-membered and five-membered rings (Figure 5). These iridoids typically feature a carboxyl group at the C-2' position and a hydroxymethyl group at the C-6' position. The carboxyl group at C-2' is often converted to a carboxymethyl group, while the hydroxymethyl group at C-6' may form an acetyl or carbonyl group. Most of the iridoids in SD were formed by iridoid glycosides, and only compounds **60**, **72,** and **77** did not form glycosides [32, 33]. In some cases, iridoids have a long-chain alkane substituted at the C-6' position or attached to a sugar group. Hydroxyl substitutions frequently occur at the C-8 position, where the hydroxyl group typically adopts a *β*-configuration. The formation of iridoid glycosides is commonly associated with a hydroxyl group at C-8. Additionally, hydroxyl substitutions can also be found at the C-4 position, with further modifications to form hydroxymethyl, hydroxyethyl, or other groups. Notably, the hydroxyl group at the C-4 position of some iridoids may react with the carboxyl group of phenylpropanoid compounds, leading to further condensation and more diverse substituents.

Compound **72** features a rare oxygen bridge linking the C-1 and C-6 positions [32]. In addition to iridoids, five triterpenoids (**82**-**86**) have been isolated from SD, all of which exist in glycosylated forms [16, 17, 34].

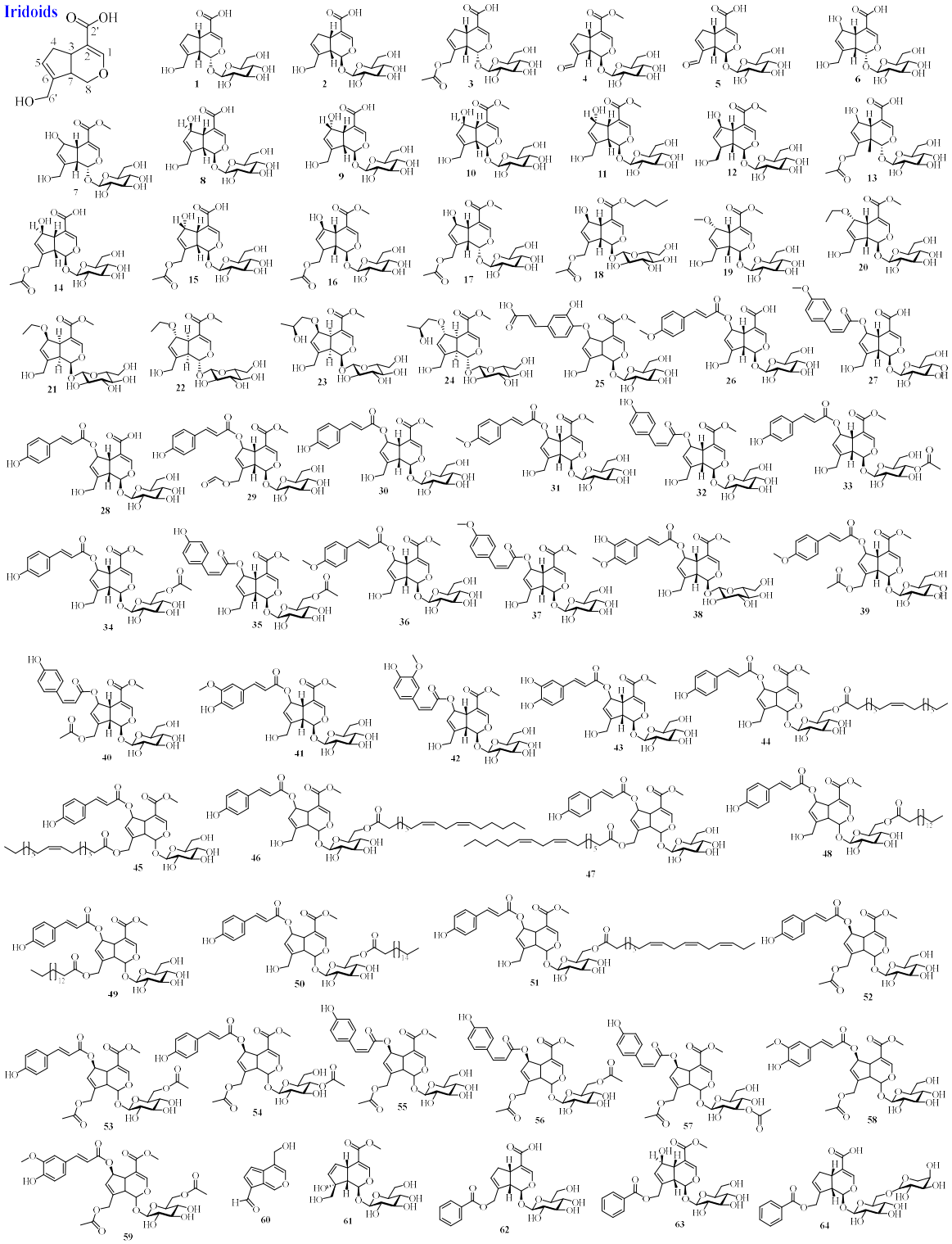

Figure 5. Structure of iridoids and triterpenes in SD *(continued..)*

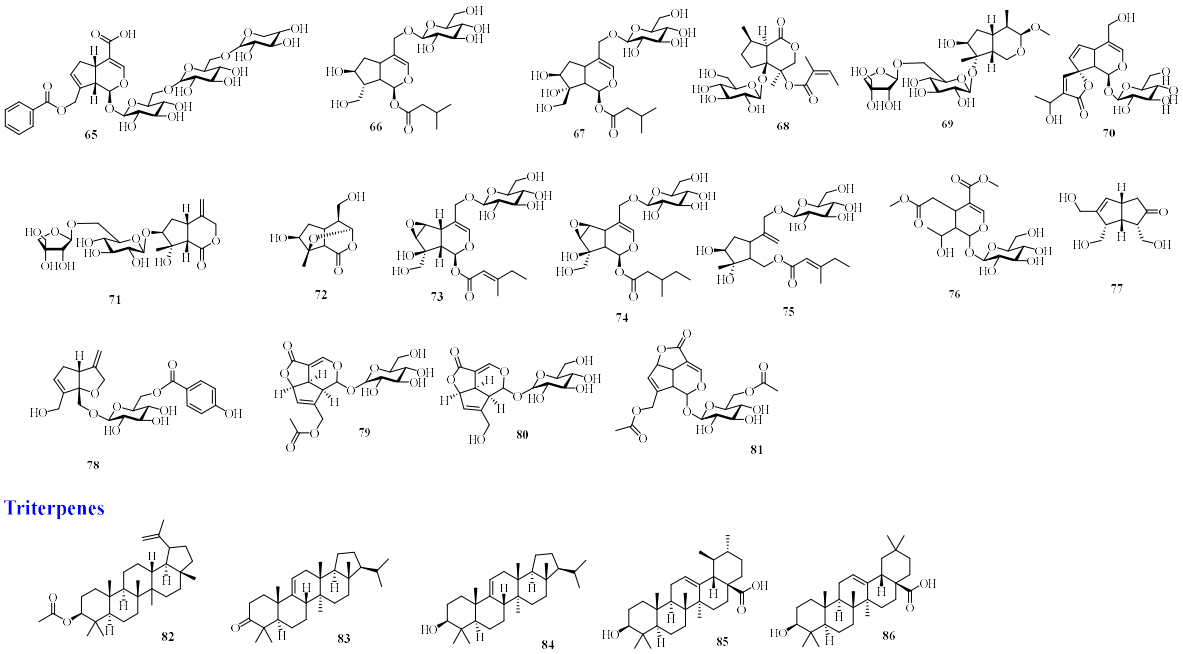

Figure 5. Structure of iridoids and triterpenes in SD

4.2. Flavonoids

Flavonoids are a widely distributed class of natural compounds in plants, characterized by a structure consisting of two aromatic rings (A and B rings) connected by a central three-carbon chain [35] (Figure 6). A total of 28 flavonoids (**87-114**) have been identified from SD. Most flavonoids are glycosylated, forming flavonoid glycosides bonded one or more sugar groups. Mostly of these sugar groups are glucose, with smaller portions being galactose or rhamnose. In terms of binding sites, the glycosyl group of flavonoid glycosides commonly binds to the hydroxyl group at the C-3 position of the B ring, while some attach to the hydroxyl groups at the C-5, C-6, or C-7 positions of the A ring. Notably, no sugar groups have been observed to bind to the hydroxyl group on the central C ring. In some cases, phenylpropanoid groups replace the sugar group, forming more diverse structural variations. Of particular interest, amentoflavone (**87**), a natural biflavone, exhibits significant anti-inflammatory, antioxidant, and anti-apoptotic effects, showing potential for therapeutic applications in a variety of diseases [36, 37].

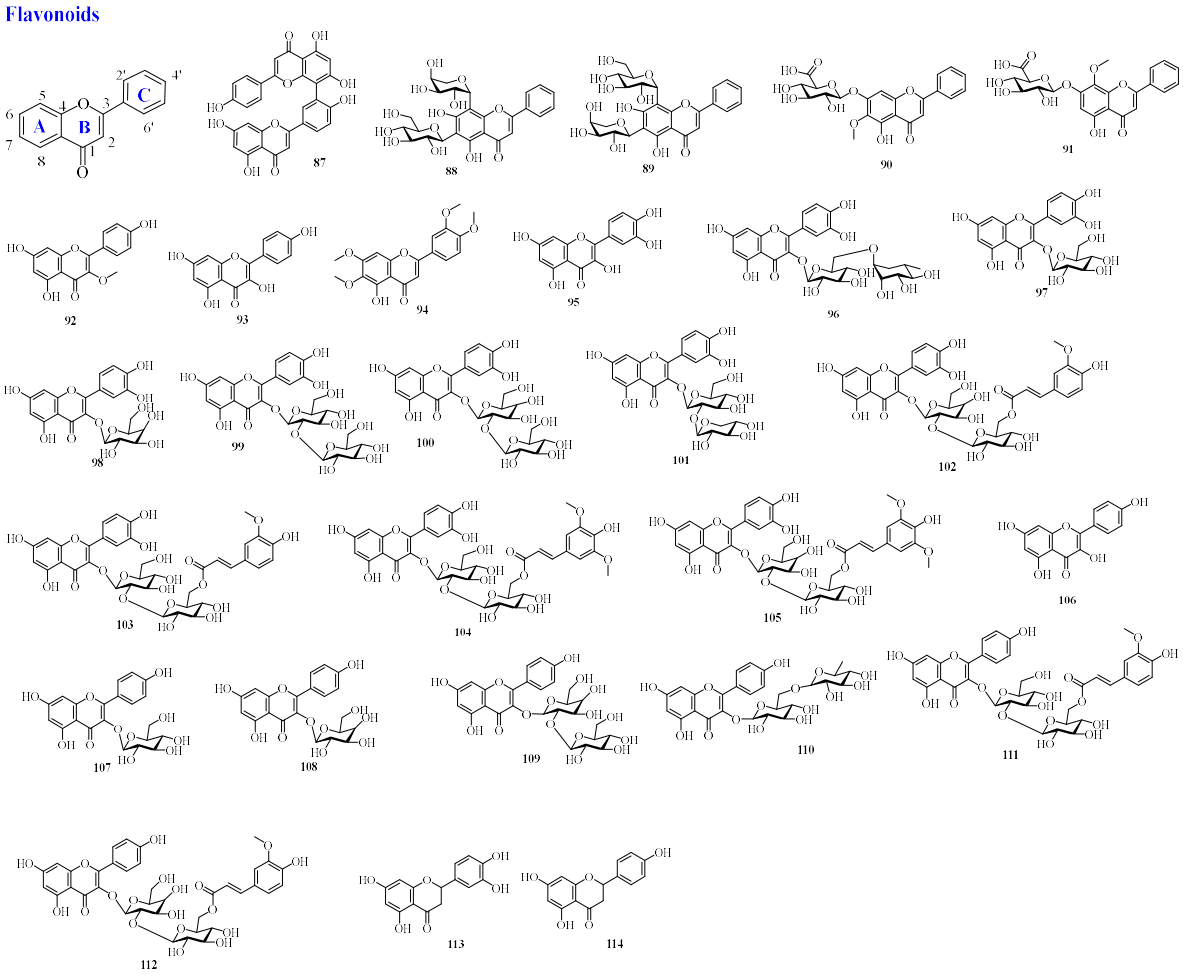

Figure 6. Structure of flavonoids in SD

4.3. Anthraquinones

Anthraquinones are secondary metabolites widely distributed in plants, known for their diverse biological activities and therapeutic applications. The core structure of anthraquinone compounds is based on anthracycline, which consists of two benzene rings connected by two common carbon atoms [38]. This conjugated system gives anthraquinones specific chemical and physical properties. To date, 46 anthraquinones (**115-160**) have been identified from SD (Figure 7). These compounds often feature hydroxyl, hydroxymethyl, methoxy, methyl, and other substituent groups on the two benzene rings. As SD belongs to the Rubiaceae family, the anthraquinones isolated from it are primarily classified as alizarin-type anthraquinones. The hydroxyl groups in these compounds are typically distributed on one side of the benzene ring, resulting in darker colors, ranging from orange-yellow to orange-red. Other notable structural variations include a special oxygen-containing five-membered ring between the C-3 and C-4 positions of compounds **153-156** and a rare oxygen-containing six-membered ring at the same positions in compounds **157-160** [19].

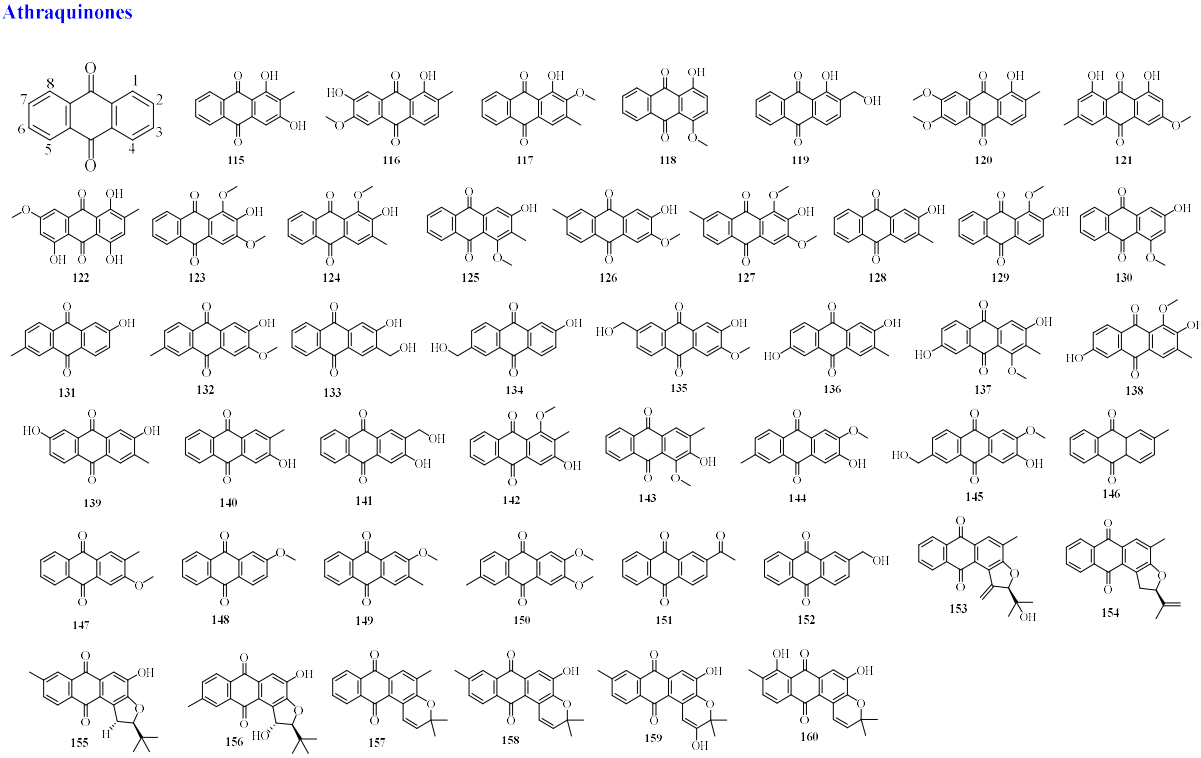

Figure 7. Structure of athraquinones in SD

4.4. Phenolic Acids

Phenolic acids are organic acids characterized by the presence of a phenol ring [39]. A total of 24 phenolic acids (**161-184**) have been isolated from SD, typically featuring hydroxyl or methoxy substitutions on the benzene ring. In particular, compounds **183** and **184** exhibit a rare structural feature: they are linked by two phenolic acid units through the formation of a cyclobutane ring [40, 41]. The structures of these compounds are shown in Figure 8.

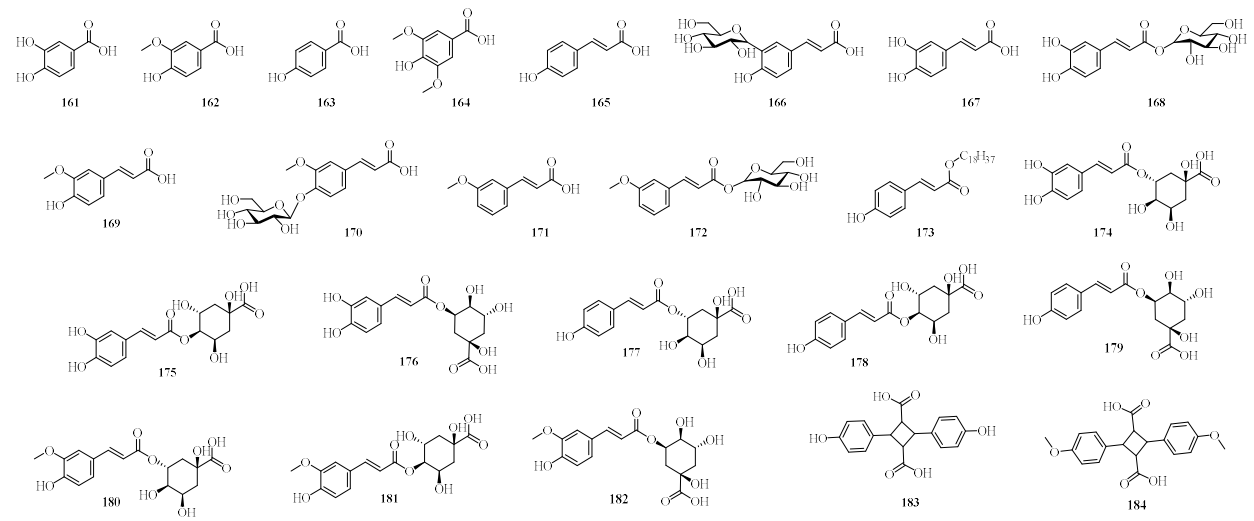

Figure 8. Structure of phenolic acids in SD

4.5. Volatile Oil Components

Volatile oil is characterized by an aromatic odor [42], and can be distilled with water vapor and are immiscible with water. 49 volatile oil components (**185-233**) have been identified from SD, including terpenoid, aromatic, and aliphatic volatile oils (Figure 9). Interestingly, despite the abundance of terpenoids in SD, the majority of the volatile oils isolated from SD are aliphatic.

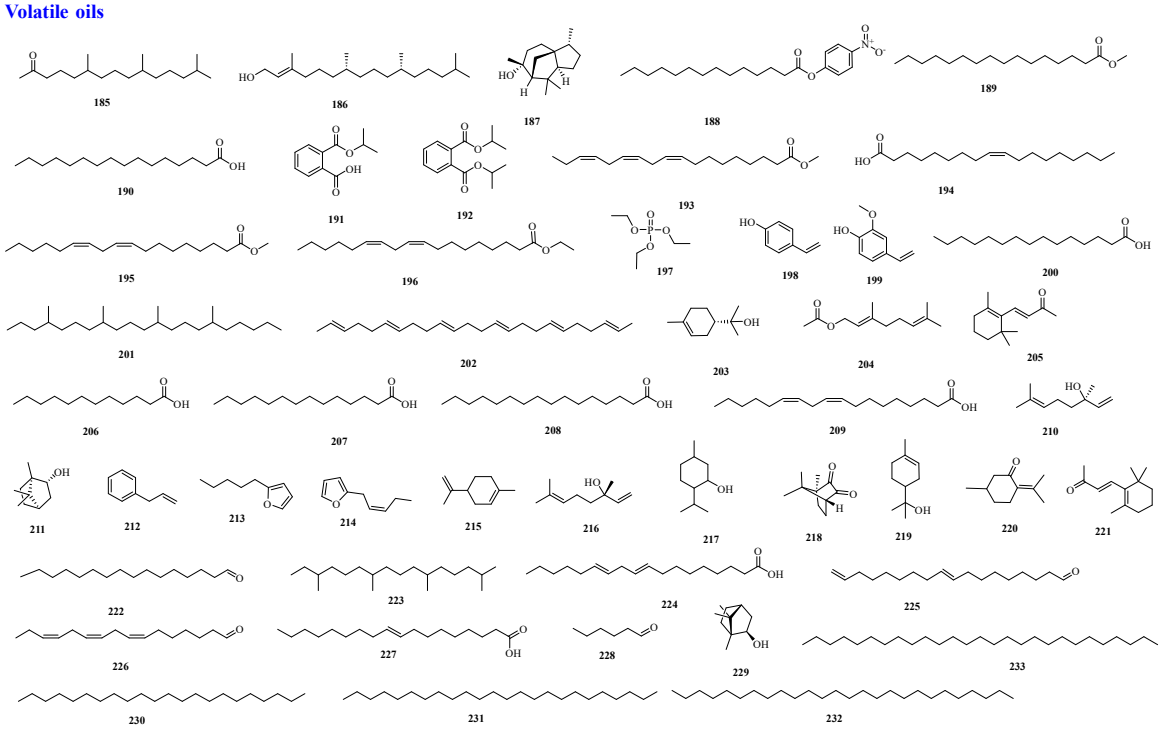

Figure 9. Structure of volatile oil components in SD

4.6. Polysaccharides

Seven polysaccharides (**234-240**) were isolated from SD (Figure 10). ODP-1 has a relative molecular mass of 20.88 kDa and is composed of mannose, rhamnose, galacturonic acid, glucose, galactose, and arabinose in a molar ratio of 0.005:0.033:0.575:1.000:0.144:0.143 [43]. HD-PS-1 has a relative molecular mass of 194.5 kDa, composed of mannose (Man), rhamnose (Rha), glucuronic acid (GlcA), glucose (Glc), and galactose (Gal) in a molar ratio of 2.1:1.4:1.1:2.7:2.8. HD-PS-2, with a relative molecular mass of 308.7 kDa, contains Man, Rha, Glc, Gal, and arabinose (Ara) in a molar ratio of 7.0:3.1:3.8:3.7:7.7. HDP1 has a relative molecular mass of 89 kDa and consists of Rha, Glu, Gal, Ara, and Man in a molar ratio of 4.31:4.16:4.49:9.22:27.8 [22]. HDP2, with a relative molecular mass of 19 kDa, consists of glucose, galactose, and mannose in a molar ratio of 2.0:1.0:1.0 [44, 45]. Lastly, HDP3 has a relative molecular mass of 6.31 kDa [46]. Notably, only the structures of compounds **235** and **236** have been further elucidated [22].

HD-PS-1 and HD-PS-2

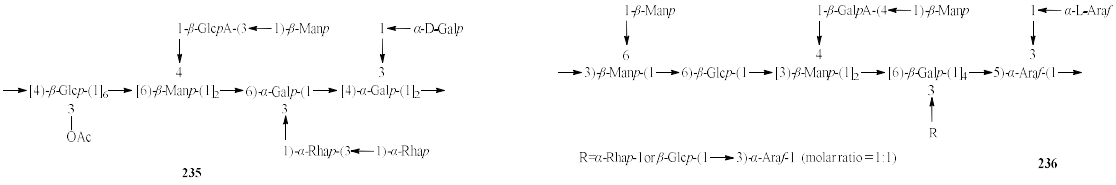

Figure 10. Presumptive structures of HD-PS-1 and HD-PS-2

4.7. Cyclic Peptides

Cyclic peptides are compounds formed through the peptide bonding of amino acids, resulting in a continuous cyclic backbone where the *N*-terminal and *C*-terminal are connected by a peptide bond. As research progresses and isolation technologies advance, the diversity of plant-derived cyclic peptides is expected to expand, showcasing significant potential in the field of medicine [47]. In this context, three novel cyclic peptides have been identified from SD, designated as CD1 (**241**), CD2 (**242**), and CD3 (**243**). The primary sequences of these peptides are as follows: CD1 is GAFLKCGESCVYLPCLTTVVGCSCQNSVCYRD, CD2 is GAVPCGETCVYLPCITPDIGCS-CQNKVCYRD, and CD3 is G-TSCGETCVLLPCLS SVLGCTCQNKRCYKD [23].

4.8. Other Compounds

In addition, 16 other compounds (**244-259**) were isolated from SD, including alkaloids, sterols and coumarin compounds. Among them, it is worth noting that five cerebrosides were isolated from SD. Specific structures are shown in Figure 11.

Others

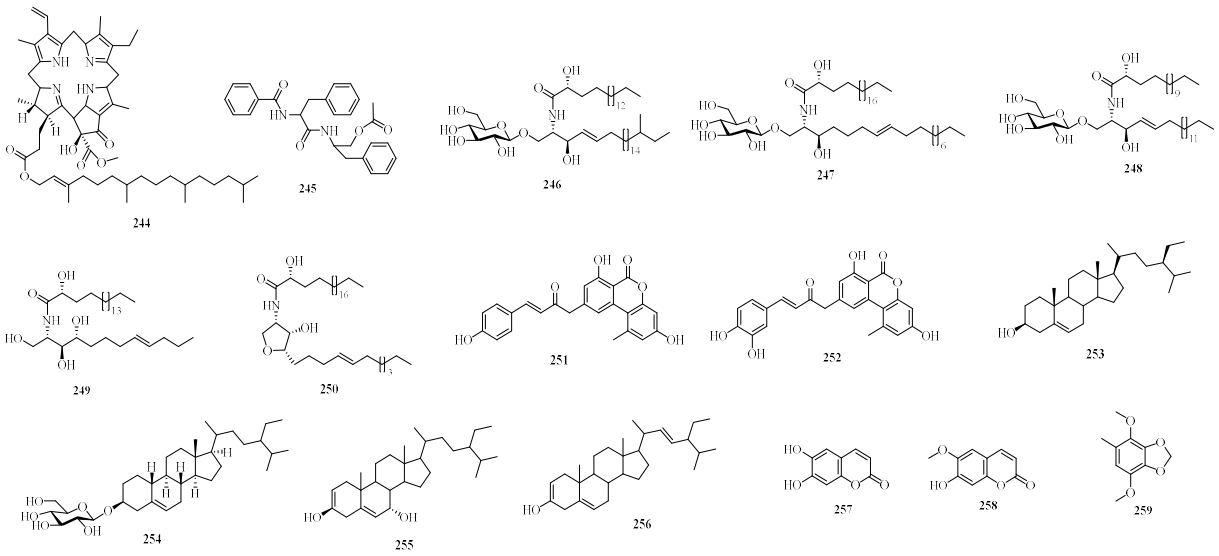

Figure 11. Structure of other compounds in SD

5. Pharmacological Activities

5.1. Anticancer Activities

5.1.1. Leukemia

The total coumarins of SD have been shown to induce apoptosis in SKM-1 cells in a dose-dependent manner, with IC_{50} values ranging from 100.66 to 104.48 μg/mL after 24 to 48 hours of treatment. The proposed mechanism of action involves the activation of caspases and the inhibition of PI3K/Akt pathway proteins, with the modulation of multiple pathways potentially attributed to the various bioactive compounds present in the extract. It has been hypothesized that this extract could have a tumor-suppressive effect on myelodysplastic syndromes or even acute myeloid leukemia, though further studies are needed to identify the specific compounds responsible for these antitumor effects [25]. Additionally, 2-hydroxy-3-methylanthraquinone (**128**) from SD has been found to enhance apoptosis in human leukemic U937 cells, likely through the activation of p-p38MAPK and the down-regulation of p-ERK1/2 [48]. Another study using mouse peritoneal macrophages demonstrated that SD, when combined with recombinant interferon-gamma (rIFN-γ), significantly increased NO and TNF-α production, with NF-κB playing a central role in these effects [49]. Furthermore, compound **128** also induced apoptosis in THP-1 cells in a time- and dose-dependent manner, with apoptosis being associated with upregulation of Fas/FasL, DR4, and TRAIL expression [50].

5.1.2. Liver Cancer

SD has shown potential in inhibiting the proliferation and migration of hepatocellular carcinoma (HCC) cells, probably through the AKT/mTOR pathway. In mouse models, SD demonstrated anticancer efficacy without causing significant weight loss or hepato-renal toxicity, offering promising possibilities for treating malignant tumors [51]. In addition, shecaocerenoside A (**246**) exhibited moderate cytotoxicity across various cell lines, while other compounds like shecaoiridoidside A (**73**) and kanokoside A (**74**) selectively affected HCT15, A459, and HepG2 cells [32]. Research by Li et al. showed that the ethyl acetate extract of SD had significant anticancer activity against HepG2 cells by increasing ROS levels and decreasing mitochondrial membrane potential, suggesting a mechanism involving mitochondrial apoptosis and death receptor pathways [52]. Moreover, SD total flavonoids were found to inhibit HCC proliferation, inducing both apoptosis and autophagy through endoplasmic reticulum stress and activation of the PERK-eIF2α-ATF4 signaling pathway [53]. Additionally, quercetin-3-*O*-sambubioside (**101**) reversed isoniazid-induced cytotoxicity and improved cell morphology, suggesting a potential hepatoprotective effect [54].

Cirrhosis is a significant risk factor for HCC, and studies have highlighted the potential of SD as a therapeutic agent for HCC. Sunwoo's investigation revealed that SD significantly enhanced apoptotic and antiproliferative activities in HCC cells, reduced their migration ability, and decreased tumor counts in a chemically induced HCC model after 28 days of treatment. Furthermore, SD lowered 18F-FDG uptake and serum levels of liver enzymes, suggesting improved liver function. Proliferating cells at the tumor site were also reduced, indicating its potential as an anticancer agent with antiproliferative and anti-metastatic properties [55]. In another study, Chen et al. evaluated the

efficacy of SD in combination with low-dose 5-FU in HepG2 cells, showing that SD significantly inhibited cell proliferation, induced S-phase delay, and downregulated E2F1 and CDK2 expression. Notably, SD enhanced the anticancer effect of low-dose 5-FU without notable toxicity [56]. Additionally, extracts from *Scutellaria barbata* and SD were found by Yang et al. to inhibit HCC growth, migration, invasion, and HBV activity, which may be attributed to luteolin and apigenin content [57]. Moreover, two anthraquinones, 2-hydroxy-3-methylanthraquinone (**128**) and 1-methoxy-2-hydroxyanthraquinone (**129**) were found to inhibit Src tyrosine kinase activity and exhibit inhibitory effects on cancer cell growth, with the former being more potent [58].

5.1.3. Lung Cancer

Lin et al. investigated the effects of SD on the metastasis of human lung adenocarcinoma A549 cells and found that it significantly inhibited cell adhesion, invasion, and migration in a dose-dependent manner. This inhibition was linked to the downregulation of matrix metalloproteinases (MMP-2 and MMP-9) and the upregulation of tissue inhibitors of metalloproteinases (TIMP-2 and TIMP-9). Additionally, SD effectively downregulated epithelial-mesenchymal transition (EMT) markers, such as N-cadherin and vimentin, while upregulating E-cadherin expression, suggesting a blockade of the epidermal growth factor receptor (EGFR)/Akt/ERK signaling pathway. SD also inhibited COX-2 protein expression, leading researchers to propose its potential as a novel anti-metastatic drug for treating non-small cell lung cancer (NSCLC) [44]. Furthermore, HDP2 (**239**) was found to inhibit A549 cell growth and induce apoptosis through the release of cytochrome c from the mitochondria, which activated caspase-9 and -3 [45]. In another study, Wang et al. demonstrated that kaempferol (**106**) significantly inhibited NSCLC cell proliferation and induced autophagy, ultimately promoting NSCLC cell death. These findings suggest SD's potential as a therapeutic agent for NSCLC [59].

Hedyoiridoidside A (**68**) was found to exhibit significant cytotoxicity against tumor cell lines (HL-60, A459, HepG2, BCG-823, CNE-2, HCT15, and PC-3 cells) with IC_{50} values ranging from 9.5 μM to 28.2 μM [60]. 2-Hydroxy-3-methyl anthraquinone (**128**) significantly inhibited the growth and colony formation of IL-6-stimulated A549 cells, increased the number of apoptotic cells, and inhibited IL-6-stimulated growth and colony formation of A549 cells, which was probably related to the IL-6-induced down-regulation of the expression of MMP-1, MMP-2 and MMP-9 genes. In addition, compound **128** decreased the expression of a series of inflammation-related cytokines (e.g., IL-6, IL-8, etc.) in the supernatant of A549 cells [61]. The analysis of Wang et al. showed that SD could promote the apoptosis of A549 cells, and the apoptosis rate in the high concentration group was significantly higher than that in the control group [62]. Su et al. used an innovative systems pharmacology platform to systematically reveal the pharmacological mechanisms of SD for NSCLC at the molecular, target, and pathway levels. The results showed that SD treatment of NSCLC activates immunity and achieves anti-inflammatory, anti-proliferative and anti-migratory therapeutic effects by modulating multiple pathways [63]. Experiments by Huang et al. showed that SD injection could significantly reduce the survival rate of lung adenocarcinoma cells cultured in vitro and inhibit the growth of lung adenocarcinoma cells by inhibiting Bcl2-promoted Bax [64].

5.1.4. Colorectal Cancer

Colorectal cancer (CRC) is one of the most prevalent malignant tumors in the gastrointestinal tract, posing a significant threat to human health [65]. TCM is increasingly recognized for its potential role in managing this disease. In a study conducted by Lai et al., the drug-resistant CRC cell line HCT-8/5 5-FU was utilized to investigate the effects of SD on cancer cell growth and metastasis. Treatment with SD effectively inhibited the viability, adhesion, migration, and invasive potential of HCT-8/5-FU cells. Furthermore, SD downregulated the expression of TGF-*β*, SMAD4, and N-cadherin, while upregulating E-cadherin expression, both at the gene and protein levels [66].

Lin et al. explored the effects of the ethanol extract of SD on the HT-29 human colon cancer cell line, finding that the extract significantly inhibited cell growth in a dose- and time-dependent manner. Treatment with the SD extract led to notable changes in cell morphology and a reduction in cell viability. Furthermore, the extract induced DNA breakage, loss of plasma membrane asymmetry, and collapse of mitochondrial membrane potential. This was accompanied by the activation of caspase-9 and caspase-3 and an increased ratio of pro-apoptotic Bax to anti-apoptotic Bcl-2, indicating that the growth inhibition of HT-29 cells was primarily mediated by mitochondrial apoptosis [67]. Another study corroborated these findings, revealing that the ethanol extract of SD not only induced apoptosis in colon cancer cells but also inhibited cell proliferation and tumor angiogenesis by regulating various signaling pathways. The proposed mechanism involves downregulating mRNA expression levels of cell cycle proteins D1, CDK 4, Bcl-2, while upregulating Bcl-2-related protein expression [68].

The ethanol extract of SD has demonstrated significant anti-tumor angiogenic activity in vivo, notably reducing intratumor microvessel density. Additionally, it inhibited the activation of the SHH signaling pathway in CRC xenograft tumors and decreased the expression of key mediators involved in CRC progression [69]. A study by Cai et al., evaluated the effect of SD ethanol extract on tumor growth was evaluated using a CRC mouse xenograft model, revealing a reduction in both tumor volume and weight without affecting the weight gain of CRC mice or causing significant adverse effects. The extract also inhibited the phosphorylation of STAT3 in tumor tissues, contributing to the suppression of tumor growth [70]. Furthermore, research indicated that the combination of SD with *Scutellaria barbata* might target the Wnt signaling pathway through the hsa_circ_0039933/hsa-miR-204-5p/wnt11 axis, thereby inhibiting the proliferation, migration, and invasion of colorectal cancer cells [71]. Li et al. found that SD significantly reduced the viability of HCT-8/5-FU cells in MTT cell proliferation assays and enhanced the retention of rhodamine-123, a substrate of the ATP-binding cassette transporter, compared to untreated controls [72]. Chen et al. further assessed the effects of SD on HCT-8 cell proliferation, migration, and invasion using MTT and Transwell assays, concluding that SD not only significantly decreased cell viability and inhibited proliferation but also attenuated the metastatic capabilities of HCT-8 cells. The extract was shown to decrease the expression of proteins in the TGF-*β* signaling pathway (including p-Smad2/3 and Smad4) while increasing E-cadherin expression, suggesting that SD may reduce the migration and invasion of colorectal cancer cells by inhibiting TGF-*β*-induced EMT [73].

Studies have shown that ursolic acid (**86**) could effectively reduce the expression of anti-apoptotic proteins, including janus kinase 2 (JAK2) and signal transducer and activator of STAT3, while also blocking the nuclear translocation of STAT3. These findings indicate that ursolic acid induces apoptosis in colorectal cancer cells primarily through the upregulation of miR-4500 and

inhibition of STAT3 phosphorylation [74]. The anticancer properties of SD were further confirmed by Li et al., who found that SD can overcome drug resistance in human CRC cells by inhibiting the PI3K/AKT signaling pathway, thus providing a basis for improving its clinical application in cancer therapy [75, 76]. Additionally, a study by Feng et al. investigated the efficacy of ethanolic extracts of SD on tumor growth using a xenograft model together with various human CRC cell lines, to explore the potential molecular mechanisms underlying its anticancer activity [77].

5.1.5. Breast Cancer

Extracts from SD play a significant role in regulating apoptosis in breast cancer cells by targeting pathways involving p-ERK, p-38, and NF-κB. They inhibit the expression of MMP-9 and intercellular adhesion molecule-1 (ICAM-1), while also modulating proteins like Bax and Bcl-2, resulting in decreased invasiveness of MCF-7 breast cancer cells. Research has shown that crude alkaloid/flavonoid extracts of SD exhibit antitumor activity against the MCF7 human breast cancer cell line [78]. Yang et al. compared the anticancer effects of aqueous extracts of SD combined with *Scutellaria barbata* at varying weight ratios on mouse breast cancer 4T1 cells. Their findings indicated that the combination was effective in inhibiting proliferation, tumor growth, colony formation, and inducing apoptosis in a concentration-dependent manner. Additionally, protein levels of PDE7B, PD-L1, *β*-catenin, and cyclin D1 were significantly reduced [79]. Ma et al. reported that high doses of SD combined with *Scutellaria barbata* inhibited proliferation and migration in three breast cancer cell lines (4T1, MDA-MB-231, and MCF-7) in vitro and reduced tumor growth in nude mice [80]. Liu et al. explored the mechanism of compound **128**, finding that it significantly increased apoptosis and caused S-phase cell cycle arrest in MCF-7 cells [81]. In a study by Yue et al., a combination of four Chinese herbs, including *Andrographis paniculata*, *Acanthopanax senticosus*, *Camellia sinensis*, and SD, was evaluated for its anti-tumor efficacy in a mouse model of metastatic breast cancer. The results showed significant reductions in mammary tumor weight, lung and liver metastases, and restoration of osteolytic bone damage after treatment with the herbal formula [82]. Zhang et al. further demonstrated that SD extracts induced notable apoptosis, S/G2-M phase arrest, and MMP disintegration in U87 cells, with dose-dependent activation of key apoptotic markers such as caspase-3, Bcl-2, and Bax [83].

5.1.6. Gastric Cancer

The Ziyin Huatan Recipe (ZYHT), which contains SD, has shown potential in the treatment of gastric cancer (GC). Researchers investigated its anti-metastatic effects by knocking out the RUNT-related transcription factor 3 (RUNX3) and inoculating lentiviral vectors into cells to establish a nude mouse model for GC lung metastasis. The results indicated that ZYHT inhibited the proliferation, migration, and invasion of GC cells in vitro by regulating the expression of metastatic proteins. Furthermore, in vivo studies demonstrated that ZYHT reduced the metastasis of GC cells to the lungs and prolonged the survival of the nude mice. Notably, the knockdown of RUNX3 partially reversed the protein expression levels associated with lung metastasis in GC cells [84]. In another study, Ou et al. explored the connection between SD and metabolic pathways through network pharmacology and bioinformatics analyses. Their in vitro experiments revealed that SD effectively inhibited the proliferation and colony formation of GC cells, reduced cell migration, and activated endoplasmic reticulum stress, suggesting a multi-faceted approach to inhibiting cancer

progression [85]. Additionally, compound **128** has been reported to exhibit inhibitory effects on the growth of various cancers. Preliminary studies indicated that it weakly induced apoptosis in GC cells, highlighting its potential as an anticancer agent [86].

5.1.7. Prostate Cancer

A network pharmacology approach has been utilized to investigate the potential mechanisms through which SD exerts its effects against prostate cancer (PCa). This study identified quercetin (**95**) and ursolic acid (**86**) as the primary components responsible for its activity. The findings suggest that SD may exert its anticancer effects by coordinating the regulation of multiple cancer-related pathways, including angiogenesis, cell differentiation, migration, apoptosis, invasion, and proliferation, thereby contributing to its therapeutic potential in PCa [87]. In a related study, the combination of SD with *Scutellaria barbata* demonstrated an inhibitory effect on the transition from G2 to M phase in prostate cancer cells. This action is likely mediated by the transcription of proteins that inhibit mitotic entry without causing severe DNA damage, highlighting a potential mechanism by which this combination therapy can suppress cancer cell proliferation [88]. Furthermore, research by Pan et al. revealed that the combination of SD and *Scutellaria barbata* also inhibited the growth of bladder cancer cells in a dose-dependent and time-dependent manner. This combination was shown to induce apoptosis by decreasing the activation of Akt and reducing the expression of anti-apoptotic proteins such as Bcl-2 and Mcl-1, suggesting a multifaceted approach to targeting cancer cell survival mechanisms [89].

5.1.8. Ovarian Cancer

Ursolic acid (**86**) has demonstrated significant cytotoxicity against ovarian cancer cells, specifically SK-OV-3 and A2780 cell lines, with IC_{50} values of approximately 50 μM and 65 μM, respectively. This compound was shown to enhance the sub-G1 apoptotic. The mechanism involves the activation of caspases and the phosphorylation of GSK 3β [90]. The traditional medicinal pairing of SD and *Scutellaria barbata* (SD-SB) has also been explored for its antitumor effects on ovarian cancer. Xu et al. utilized network pharmacology and molecular biology to analyze the mechanisms underlying SD-SB's action. Their results identified key targets involved in inhibiting the growth and migration of ovarian cancer cells, including the EGFR, MAPK1, vascular endothelial growth factor A (VEGFA), and PIK3CG [91]. In addition, Zhang et al. found that SD significantly inhibited the growth of A2780 ovarian cancer cells and induced apoptosis, likely through a mitochondrial apoptosis pathway. The study also noted that SD reduced the migration of ovarian cancer cells by down-regulating MMP-2 and MMP-9, which are associated with tumor invasion and metastasis [92]. Lee et al. further investigated the molecular mechanisms of SD extracts in combination with cisplatin. They found that the combination therapy was more effective in reducing the survival of A2780cis cells compared to cisplatin alone. This suggests that SD may help promote apoptosis in cisplatin-resistant ovarian cancer cells by regulating the expression of key genes such as KDM1B and DCLRE1B, thereby enhancing the efficacy of conventional chemotherapy [93].

5.1.9. Nasopharyngeal Cancer

SD has emerged as a promising adjuvant therapy for advanced nasopharyngeal cancer, with studies highlighting its significant anti-tumor effects [94]. Research on HDP1 (**238**) reveals that it inhibits the proliferation of Hep2 human laryngeal squamous carcinoma cells in a time- and dose-

dependent manner, inducing cell cycle arrest at the G0/G1 phase. Moreover, treatment with HDP1 for 24 hours leads to significant apoptosis in Hep2 cells, characterized by increased cleavage of caspases-3, -8, and -9, alongside a reduction in Bcl-2 protein expression, which enhances its pro-apoptotic effects. Additionally, HDP1 inhibits cell migration and decreases the expression of MMP-2 and urokinase-type plasminogen activator (μPA), crucial for tumor invasion and metastasis [95]. Network pharmacology analyses further reveal that SD impedes the proliferation, migration, and invasion of nasopharyngeal carcinoma cells by down-regulating AKT1 and up-regulating VEGFA [96].

5.1.10. Cervical Cancer

SD has demonstrated significant potential in the treatment of cervical cancer, as evidenced by various studies. Qian et al. constructed an active ingredient-target network to identify key targets associated with SD for cervical cancer treatment, highlighting *β*-sitosterol (**254**) and quercetin (**95**) as its primary active components. By analyzing and enriching the targets, they assessed the prognostic value of these core target genes through survival analysis, providing a theoretical foundation for further investigation into SD's pharmacological effects and clinical applications [97]. Complementing this, Zhang et al. indicated that SD effectively inhibited cervical cancer cell growth and induced apoptosis, demonstrating its positive therapeutic effects in the management of cervical cancer. Together, these studies underscore the potential of SD as a valuable therapeutic agent in the fight against cervical cancer [98].

5.1.11. Cancer Immunotherapy

Recent studies have highlighted the promising anticancer properties of SD extracts. The ethyl acetate extract of SD has been shown to induce apoptosis in tumor cells, particularly in Hep3B cells, by upregulating pro-apoptotic factors such as Bax, cytoc, and PARP, while downregulating the anti-apoptotic protein Bcl-2. Furthermore, activation of the JNK/Nur77 pathway was observed, indicated by increased levels of phosphorylated JNK (p-JNK) and Nur77 (p-Nur77), suggesting a mechanistic involvement in the apoptotic process [99]. Additionally, the ethanol extract of SD, which is rich in ursolic acid (**86**), exhibited significant cytotoxicity against GCa cells, leading to increased cytotoxic effects and inhibited colony formation [100]. Compound **128** demonstrated substantial inhibitory effects on various tumors. Jing et al. explored its effects on osteosarcoma cells, revealing that HMA regulates MYC expression through the PI3K/AKT signaling pathway, inhibiting cell proliferation and DNA damage repair mechanisms. Their findings, supported by RNA sequencing, immunohistochemistry (IHC), and Western blotting studies, established a critical link between MYC, CHK1, and RAD51 in the context of osteosarcoma progression. These results collectively underscore the therapeutic potential of SD extracts in cancer treatment [101].

Recent investigations into the immunostimulatory effects of SD on cytokine-induced killer (CIK) cells reveal promising results for cancer therapy. In a study utilizing various concentrations of SD (10, 50, and 100 μg/mL), researchers found that SD significantly increased the proportion of $CD3^+CD56^+$ CIK cells, indicating enhanced activation of these immune cells. However, there was no notable change in the proportions of $CD4^+$, $CD8^+$, or $CD4^+CD25^+$ CIK cells. Furthermore, SD-treated CIK cells demonstrated a heightened capacity to kill tumor cells and exhibited increased production of interferon-γ and tumor necrosis factor-α compared to untreated CIK cells. In mouse

models, the combination of SD and CIK cells showed a stronger inhibitory effect on tumor growth, underscoring the potential of SD in enhancing immune responses against cancer [102]. In addition to its immunomodulatory effects, the ethanolic extract of SD has been reported to inhibit lymphangiogenesis, a crucial factor in cancer metastasis regulated by VEGF-C. Li et al. demonstrated that SD inhibits VEGF-C-mediated lymphangiogenesis in CRC, positioning it as a multipurpose anticancer agent for clinical applications [103]. The regulatory impact of SD on CRC cell proliferation and apoptosis was also assessed, with findings indicating that SD downregulated the expression of key proteins such as cyclin D1, CDK 4, and Bcl-2. Moreover, SD treatment was associated with decreased AKT and ERK [104].

5.1.12. Other Cancers

The Qingyihuaji decoction containing SD has demonstrated clinical efficacy in treating pancreatic cancer. A study by Yang et al. used a network pharmacology approach was utilized to investigate its therapeutic mechanisms. The results of qRT-PCR indicated that the Qingyihuaji decoction significantly inhibited the mRNA expression of ICAM1, vascular cell adhesion molecule 1 (VCAM1), and Bcl-2, while increasing the expression of heme oxygenase 1 (HMOX1) and Bcl-2. Additionally, immunoblotting analyses revealed alterations in critical signaling pathways, including the PI3K/AKT/mTOR, Keap1/Nrf2/HO-1/NQO1, and Bcl-2/Bax pathways, suggesting a multifaceted mechanism of action [105]. Furthermore, research by Lv et al. explored the tumor-inhibitory effects of a combined aqueous extract of SD-SB in an equal weight ratio. This combination exhibited a notably low IC_{50} of 0.43 mg/mL, indicating potent inhibition of cell proliferation compared to other aqueous extracts. These findings highlight the potential of both the Qingyihuaji decoction and the SDSB combination as effective therapeutic options for pancreatic cancer treatment [106].

Research has demonstrated that SD effectively inhibits angiogenesis in the chick embryo chorioallantoic membrane model in vivo. Additionally, SD was found to reduce the proliferation of human umbilical vein endothelial cells, a key component in the formation of new blood vessels, in a dose- and time-dependent manner. This anti-angiogenic effect is associated with the down-regulation of VEGF at both the mRNA and protein expression levels, suggesting that inhibition of tumor angiogenesis is a significant mechanism through which SD contributes to cancer therapy [107]. Moreover, Lu et al. investigated the anti-tumor effects of SD-SB at various concentrations in vitro. Their findings revealed that the combination significantly inhibited tumor cell apoptosis in rat models, along with a reduction in the expression of key proteins such as phosphorylated EGFR, heat shock protein 90, and Bcl-2 [108].

5.2. Antioxidant Capacities

The butanol extract of SD was shown to affect nematode growth and development by stimulating growth, reducing the deposition of aging pigments, and increasing the accumulation of active age pigments. Additionally, it enhanced the activities of SOD and GSH-Px, while decreasing ROS levels. Furthermore, the extract mediated lifespan extension through the upregulation of gene expression of daf-16, gst-4, sod-3, and hsp12.6, along with the downregulation of daf-2. This finding suggests a potential role for these genes in the longevity induced by the butanol extract of SD in *Caenorhabditis elegans* [26]. Additionally, studies showed that the total flavonoids from SD effectively reduced MMP loss and cytochrome c release in hepatotoxic cells, subsequently

inhibiting the activation of the caspase-3/caspase-9 cascade. The levels of ASK1 and phosphorylated p38 (p-p38) were diminished through the upregulation of the sulfur oxidoreductase Trx1 and the reductase TrxR1 in the amentoflavone (**87**) group. These results suggest that the antioxidant effects of flavonoids may stem from reduced ROS levels, achieved by increasing Trx1 and TrxR1, which in turn inhibits the upstream impacts of the H_2O_2-induced pathway [109]. Furthermore, SD demonstrated a preventive effect on the oxidation of low-density lipoprotein (LDL) cholesterol, contributing to their medicinal therapeutic effects by directly inhibiting oxidation [110].

5.3. Anti-hepatic Injury Activities

Zhao et al. investigated the mechanism by which SD mediates the detoxification of aflatoxin B1 (AFB1). In their study, 144 one-day-old male broilers were randomly assigned to treatment groups and fed either AFB1 or AFB1 combined with SD for two weeks. The results indicated that AFB1 treatment caused significant liver injury and resulted in reductions in body weight gain, feed intake, feed conversion ratio, serum albumin, and total protein, with decreases ranging from 6.2% to 20.7% compared to the control group. Additionally, AFB1 induced hepatic swelling, necrosis, and severe vacuolar degeneration in the chicks. However, supplementation with SD significantly attenuated AFB1-induced damage to hepatic glutathione peroxidase activity, protein carbonyl levels, and exo-AFB1-8,9-epoxide [27]. Moreover, SD demonstrated a beneficial impact on AFB1-induced liver injury in ducks. It mitigated the decline in growth performance and alleviated AFB1-induced histopathological changes in duck livers, as well as improved the liver index [111]. Scholars utilized cytokine expression, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, survival rates, and histological analysis to assess the effects of SD decoction on LPS/GALN-induced acute severe hepatitis in mice. Metabolomic analysis revealed that the proportion of carbohydrates in the SD group was lower than that in the LPS/GALN group, highlighting the potential of SD decoction for treating carbohydrate metabolism disorders in the liver of mice [112]. Chen et al. conducted a long-term toxicity assessment of SD in SD rats to evaluate its safety. The treatment groups received different doses of CGSD-E, ranging from 10 to 50 times the human clinical dose. The results indicated that the treated rats generally remained in good condition throughout the long-term toxicity test; however, as a result, continuous administration of CGSD-E showed reduced body weight and food intake, particularly in male rats [113].

5.4. Anti-inflammatory Activities

5.4.1. Arthritis

Screening using network pharmacological methods identified *β*-sitosterol (**254**), quercetin (**95**), kaempferol (**106**), and 2-methoxy-3-methyl-9,10-anthraquinone (**149**) as the key components of SD for the treatment of rheumatoid arthritis (RA). The results indicated that SD may exert anti-RA effects by modulating central targets through the PI3K/AKT signaling pathway [28]. Lou et al. investigated the anti-inflammatory effects of SD and its potential mechanisms in IL-1*β*-induced inflammatory conditions. Network pharmacology results revealed that Bax, Bcl-2, CASP3, and JUN are key candidate targets of SD for the treatment of osteoarthritis. Molecular docking studies indicated that *β*-sitosterol (**254**) in SD exhibits strong binding affinity to CASP3 and PTGS2[114]. In vitro experiments demonstrated that SD pretreatment significantly inhibited the expression of IL-

1*β*-induced pro-inflammatory factors, including COX2, iNOS, IL-6, TNF-*α*, and PGE2. Furthermore, SD was found to alleviate cartilage degeneration in a mouse model of knee osteoarthritis [114]. Zhu et al. explored the efficacy of SD in the treating rheumatoid arthritis through animal experiments. Rats with collagen-induced arthritis were administered either SD decoction or identified absorbable compounds. Compared to the model group, the treated rats showed symptomatic relief and a reduced inflammatory response. Moreover, the arthritis index and serum levels of TNF-*α* and IL-6 were significantly reduced in the SD-treated rats compared to untreated model rats [115].

5.4.2. Kidney Inflammation Activities

The anti-inflammatory and hypolipidemic effects of SD were investigated using a nephrotic syndrome rat model. Following SD treatment, the levels of all indices, except for BUN and serum creatinine (Scr), decreased, indicating improvements in renal function and dyslipidemia. SD also reduced the inflammatory response by inhibiting the mRNA expression of the NF-κB pathway, along with the expression of p50 and p65 proteins [130]. Researchers have also used the MRL/lpr model mice, which reflect the spontaneous development of nephritis, to assess the protective activity of SD extracts and investigate potential influencing factors. Treatment with SD extracts improved renal expression of STAT3, IL-17, Ly6G, and myeloperoxidase (MPO), as well as neutrophil NETosis. At the same time, urinary protein levels and inflammatory cell infiltration were reduced, and the formation of glomerular mesangial cells was inhibited [116]. Additionally, another study demonstrated that SD aqueous extracts are effective in treating lupus nephritis by reducing autoantibody production and the secretion of IL-6 and IFN-γ. The extracts also inhibited the deposition of IgG and complement component 3, thereby mitigating the progression of glomerular lesions and glomerular injury in MRL/lpr patients [117]. Wang et al. indicated that SD upregulated OATs via HNF1α, resulting in alleviated renal fibrosis [118].

Ye et al. investigated the protective effects of SD against LPS-induced renal inflammation. The results showed that the aqueous extract of SD (5.0 g/kg) significantly protected renal tissues by inhibiting the production of TNF-*α*, IL-1*β*, IL-6, and monocyte chemotactic protein-1 (MCP-1), while promoting the production of IL-10 in both serum and renal tissues [119]. Chen et al. investigated the anti-inflammatory effects of SD in an in vitro inflammation model using LPS-stimulated RAW 264.7 cells. Their results demonstrated that SD inhibited the inflammatory response and significantly reduced LPS-induced expression of iNOS, TNF-*α*, IL-6, and IL-1*β* in a concentration-dependent manner without causing cytotoxicity. Furthermore, SD suppressed the mRNA expression of iNOS, TNF-α, IL-6, and IL-1*β* in LPS-stimulated RAW 264.7 cells. The authors hypothesized that SD may exert its anti-inflammatory activity by inhibiting the NF-κB and MAPK signaling pathways [120].

5.4.3. Other Inflammation Activities

The ethyl acetate fraction of the aqueous extract of SD-SB was found to be the most potent inhibitor of LPS/IFN-*α* stimulated serum nitrite accumulation in RAW 264.7 cells. Further investigations revealed that the aqueous extract inhibited the expression of iNOS and IL-1α in a concentration-dependent manner, while promoting the expression of HO-1 and PPAR-*α*. This anti-inflammatory activity is likely mediated through its inhibitory effects on the c-JNK signaling pathway and miR-155 expression [136]. 2-Hydroxymethyl anthraquinone (**152**) has been reported

to possess broad-spectrum anti-inflammatory properties. It was shown to reduce LPS-induced pulmonary edema, myeloperoxidase activity, and inflammatory cytokine production in mouse models of acute lung injury [137]. Kim et al. explored the effects of hentriacontane, a component of SD, on LPS-induced inflammatory responses in murine peritoneal macrophages. Their results indicated that the anti-inflammatory effects of SD were mediated by modulating the activation of NF-κB and caspase-1. Additionally, SD improved the expression of inflammatory mediators, including TNF-*α*, IL-6, PGE2, COX-2, and iNOS [138].

Administration of the aqueous extract of SD to mice resulted in an increase in pain threshold and a decrease in inflammatory lesions and inflammatory cell infiltration compared to the model group [121]. An in vivo animal model was utilized to explore the protective effects of SD against chronic airway inflammation and its underlying mechanisms. LPS-induced mice were treated with SD via gavage. The results indicated that levels of IL-1*β*, TNF-*α*, and TGF-*β* were significantly decreased in the bronchoalveolar lavage fluid of SD-treated mice, while the level of IL-10 was also significantly reduced compared to the model group. Histological examination of lung tissue demonstrated that SD treatment alleviated airway inflammation [122]. Diffusadoids B (**45**), D (**47**), and F (**49**) were evaluated for their anti-inflammatory activity in LPS-induced RAW 264.7 cells, which exhibited significant inhibitory effects on NO production, with IC_{50} values of 5.69, 6.16, and 6.84 μM, respectively. Structure-activity relationship studies suggested that the long-chain aliphatic group located at C-10 may be the key moiety contributing to their anti-inflammatory activities [123]. Additionally, a series of quinones isolated from SD, particularly anthraquinones with 2-isopropyldihydrofuran or 2,2-dimethylpyran moieties, demonstrated promising anti-inflammatory activities by inhibiting superoxide anion generation and elastase release [19].

5.5. Anti-Alzheimer's Disease Activities

The researchers used the CL4176, CL2006, and CL2355 transgenic strains to investigate the in vivo A*β* protective effects mediated by the n-butanol extract of SD and its potential mechanisms. The study demonstrated that SD reduced paralysis, ROS accumulation, and AChE activity. It also inhibited chemotactic deficits induced by neuronal A*β* expression and increased SOD activity [29]. Park et al. evaluated the inhibitory activity of SD against neurodegenerative diseases, particularly Alzheimer's disease (AD). They found that quercetin-3-*O*-[2-*O*-(6-*O*-*E*-feruloyl)-*β*-D-glucopyranosyl]-*β*-D-glucopyranoside (**103**) exhibited the strongest inhibitory effect on cholinesterase, *β*-site amyloid precursor protein cleaving enzyme 1 (BACE1), and advanced glycation end-products (AGEs) formation. Notably, in the BACE1 inhibition assay, this compound demonstrated higher inhibitory activity than the positive control, quercetin, indicating its potential as a natural therapeutic agent for the treatment of AD [124]. Li et al. evaluated the AChE inhibitory activity of four different extracts of SD, finding that the n-butanol extract exhibited significant inhibitory activity against AChE, warranting further investigation [125].

5.6. Other Activities

In a separate study, Lee et al. showed that SD pretreatment significantly reduced the escape latency in scopolamine-treated ICR mice during the Morris water maze test. Further investigation revealed that SD treatment restored scopolamine-induced amnesia in the ICR mouse model, suggesting its potential as a therapeutic agent for memory-related disorders [126].

Asperuloside (**79**) has been reported to potentially ameliorate chemotherapy-induced myelosuppression. One study indicated that compound **79** significantly increased the body weight of cyclophosphamide (CTX)-induced mice, increased the number of hematopoietic progenitor cells, and elevated the expression of leukocytes, erythrocytes, platelets, and C-kit in bone marrow. Furthermore, compound **79** promoted the expression of autophagy-related proteins Beclin1 and LC3-II/I in CTX-treated mice. It also regulated the proteins involved in the AMPK/mTOR pathway, thereby alleviating the myelosuppressive effects induced by CTX treatment. Mao et al. found that SD had a significant effect on the development of dengue virus and Zika virus and Japanese encephalitis virus replication and reduced viral RNA levels in a dose-dependent manner at concentrations ranging from 0.1 to 10 mg/mL [30].

Researchers investigated the antimicrobial and biofilm inhibitory activities of SD extracts against respiratory tract infections. The results showed that the SD extract significantly inhibited its growth in a dose-dependent manner. Additionally, the mRNA level of luxS, a gene associated with biofilm formation in *Haemophilus influenzae*, was notably reduced after treatment. Furthermore, the auto-inducer concentration in the culture supernatant decreased significantly in a dose-dependent manner within two hours of adding the extract [127].

All the pharmacological effects of this genus are summarized in Table 2

Table 2. Pharmacological activities of SD

Pharmacological	Models	Dosage	*In Vitro*/*In Vivo*	Pathway or possible target site	Ref.
Anticancer	SKM-1 cells	0, 25, 50, 75, 100 and 125 μg/mL	*In Vitro*	PI3K/Akt pathway, caspase-3-8,-9↑	[25]
	U937 cells	0, 20, 40 and 80 μM	*In Vitro*	p-ERK1/2↓, p-P38mapk, caspase-3↑	[48]
	THP-1 cells	50 μM	*In Vitro*	Fas/FasL, DR4, TRAIL, caspase-8↑	[50]
	Hep-G2 cells	20 mg/mL	*In Vitro*	AKT/mTOR pathway;	[51]
	A459, HepG2, PC-3, CNE-2 and BCG-823 cells	1.0 μM to 300 μM	*In Vitro*	-	[32]
	HepG2, Hep3B, HCCLM3 cells	12.5, 20, 25 μg/mL	*In Vitro*	PERK-eIF2*α*-ATF4 signaling pathway	[53]
	Rats	200 mg/mL	*In Vivo*	ALT、AST、ALP↓	[55]
	HepG2 cells	0, 1.25, 2.5, 5 and 10 mg/mL	*In Vitro*	CDK2, cyclin E and E2F1↓	[56]
	A549 cells	0, 20, 40 and 80 μM	*In Vitro*	JAK2/STAT3 pathway; MMP-1, MMP-2, MMP-9, IL-6, G-CSF, IL-6R, IL-8, MCP-1, RANTES, TNF-*α*↓	[61]
	mouse peritoneal macrophages	1 mg/mL	*In Vitro*	TNF-*α*,NO↑	[57]
	A549 cells	25, 50 and 100 μg/mL	*In Vitro*	EMT, N-cadherin and vimentin↓ E-cadherin, TIMP-2, TIMP-9↑	[44]
	A549 cells	25、100 and 200 μg/mL	*In Vitro*	caspase-9, -3↑, Bax/Bcl-2 ↓	[45]
	A549 and H1299 cells	0, 10, 20, 40 and 80 μmol/mL	*In Vitro*	PI3K/AKT/mTOR signaling pathway	[59]
	CD8 and Treg cells	20 mg/kg	*In Vitro*	PI3K-AKT, MAPK pathway	[63]
	HT-29 cells	0, 1, 3 and 5 mg/mL	*In Vitro*	caspase-9, caspase-3, Bax, Bcl-2↑	[67]
	HT-29 cells	1, 3 and 5 mg/mL	*In Vitro*	IL-6/STAT3 signaling pathway; STAT3↑, Cyclin D1, Bcl-2↓	[68]

HCT-8/5-FU cell	0, 0.5, 1 and 2 mg/mL	*In Vitro*	E-cadherin↑, TGF-*β*, SMAD4 and N-cadherin↓	[66]
nude mouse and HT-29 cells	3 g/kg	*In Vitro* and *in Vivo*	STAT3 pathway	[69]
CRC mice	6 g/kg	*In Vivo*	STAT3 pathway; p21, Bax↑, Cyclin D1, CDK4, Bcl-2↓	[70]
HT-29, SW620 and HCT116 cells	1 mg/mL	*In Vitro*	hsa_circ_0039933/hsa-miR-204-5p/wnt11 axis	[71]
HCT-8/5-FU cells	0, 0.5, 0.75, 1, 1.5 and 2 mg/mL	*In Vitro*	P-gp, ABCG2↓	[72]
HCT-8 cells	0, 0.25, 0.5, 1 mg/mL	*In Vitro*	N-cadherin, vimentin ↑ TGF-*β*, p-Smad2/3, Smad4, E-cadherin↓	[73]
HCT116 cells	0, 20, 40 μM	*In Vitro*	miR-4500↑, STAT3↓	[74]
HT-29 cells	0, 0.5, 1 and 2 mg/mL	*In Vitro*	Bax↑, COX-2, Inos, eNOS, HIF-1*α*, Bcl-2↓	[77]
MCF-7 cells	0, 10, 30, 50, 70 and 100 μg/mL	*In Vitro*	ERK1/2 MAPK pathways; Bax↑, Bcl-2, MMP-9, ICAM-1, p-p38↓	[78]
4T1 cells	25 g/kg	*In Vitro*	cAMP, miR-200c ↑ PDE7B, PD-L1, β-catenin, cyclin D1↓	[79]
MCF-7 cells	30 μM	*In Vitro*	Ca^{2+}/calpain/caspase-4 pathway	[81]
U87 cells	0, 4, 8 mg/mL	*In Vitro*	caspase-3, Bcl-2, Bax, ERK↓	[83]
SGC-7901 cells	25, 50 and 100 μg/mL	*In Vitro* and *in Vivo*	RUNX3↑	[84]
GBC cell	25, 50, and 100 μg/mL	*In Vitro*	PI3K/Akt, Wnt, HIF-1, focal adhesion, microRNAs pathway	[86]

SK-OV-3, A2780 cells	0, 5, 10, 20 μM	*In Vitro*	Bax, cytoc, PARP, r183/Tyr185↑ PARP, caspase-9 and -3↓, JNK/Nur77 pathway	[90]
A2780 cells	100 mg/mL	*In Vitro*	EGFR, MAPK1, VEGFA, and PIK3CG pathway	[91]
A2780 cells	0, 50, 100, 200, 300, 400, 600, 800 μg/mL	*In Vitro*	mitochondria-associated apoptotic pathway; caspase 3/9↑, MMP-2/9, Bcl-2 ↓	[92]
A2780cis cells	40 μg/mL and 160 μg/mL	*In Vitro*	DCLRE1B ↓	[93]
Hep3B cells	50–400 μg/mL	*In Vitro*	Bax, cytoc, PARP, r183/Tyr185↑ Bcl-2 ↓; JNK/Nur77 pathway	[94]
Hep2 cells	400 μg/mL	*In Vitro*	caspase-3, caspase-8, caspase-9↑ MMP-2, μPA, Bcl2↓	[95]
NPC cell	45 g/60 kg	*In Vitro*	AKT1 and VEGFA pathways	[96]
GCa cells	5, 10, and 15 μM	*In Vitro*	ERRK1/2 ↓	[100]
OS cells	0, 50, 100, and 200 μmol/L	*In Vitro*	PI3K/AKT, MYCCHK1-RAD51 signaling pathway	[101]
CIK cells, mouse	10 μg/mL	*In Vitro* and *in Vivo*	interferon-γ, TNF-*α*↑	[102]
CRC cells	0, 0.125, 0.25, 0.5 and 1 mg/mL	*In Vitro*	PI3K/AKT, ERK and STAT3 pathway; VEGF-C↓	[103]
PANC-1 and MIA PaCa-2 cells	0, 2, and 4 mg/ mg/mL	*In Vitro*	HMOX1, NQO1↑ ICAM1, VCAM1, Bcl2 ↓	[105]
Lewis-lung-carcinoma-bearing mouse	30 g/kg	*In Vivo*	NLRP3, procaspase-1, caspase-1, PRAP, Bcl-2 , D1, NF-Kb, ERK, JNK, p38 MAPK↓	[106]

	SW620 cells	0, 150, 300 and 500 μg/mL	*In Vitro*	Survivin, Cyclin D1, Bcl-2, AKT, ERK↓	[104]
	HT-29 cells	400 mg/mL	*In Vitro*	VEGF-A, CAM↓	[107]
Antioxidant	C. elegans	0.25, 0.5 mg/mL	*In Vivo*	daf-16, gst-4, sod-3, hsp12.6 , SOD, GSH-Px↑ ROS↓	[108]
	HL-02 cells	62.5, 125, 250 μmol/L	*In Vitro*	ASK1/p38 MAPK pathway; caspase-3/caspase-9, ASK1 , p-p38 l, Trx1 ,TrxR1↓	[109]
Anti-hepatic injury	male broilers	500, 1000 mg/kg	*In Vivo*	NRF2/ARE signaling pathway; quinone oxidoreductase-1, heme oxygenase-1↑, AFBO↓	[27]
	male Pekin ducks	200 mg/kg	*In Vivo*	Nrf2, HO-1, NQO1↑, AFB1-DNA↓	[111]
	mice	5 g/kg	*In Vivo*	biosynthesis of unsaturated fatty acids, alanine, aspartate and glutamate metabolism	[112]
	SD rats	450.72 mg/kg; 312.04 mg/kg	*In Vivo*	-	[113]
Anti-inflammatory	mouse	50, 100 mg/kg	*In Vivo*	IL-1β, TNF-α, and TGF-β↓	[122]
	mouse osteoarthritis	0, 0.25, 0.5, 1, 2, 4, and 8 mg/mL	*In Vitro*	MAPK pathway;	
	NS rat		*In Vivo*	IL-1β ↑, COX2, iNOS, IL-6, TNF-α, PGE2↓	[114]
	Arthritis Model Rats	2.7 mg/g	*In Vivo*	TNF-α, IL-6,↓	[115]
	MRL/lpr model mice	1 g/mL	*In Vivo*	STAT3/IL-17signaling pathways	[116]
	MRL/lpr lupus mouse	1 g/mL	*In Vivo*	IL- 6/STAT3 pathway	[117]
	Balb/C mice	14 and 28 mg/kg	*In Vivo*	OATs, HNF1α↑	[118]

	RAW 264.7 cells	0, 25, 50, 100, 200, 400 and 800 μg/mL	*In Vitro*	TNF-α, IL-6, IL-1β, iNOS, NO↓	[120]
	RAW264.7 cells	10, 50, 100, and 200 μg/mL	*In Vitro*	JNK signaling pathway; NOS and IL-1↓	[208]
	ALI mice	0-160 μg/mL	*In Vivo*	SOD, GSH↑ MDA, NO, TGF-*β*, TNF-*α*, IL-6, IL-1*β*↓	[209]
	C57BL/6 mice	0.01-1 mg/mL	*In Vivo*	TNF-*α*, IL-6, PGE2, COX-2 ↓	[210]
	C57BL/6 mice	0.2 mg/mL	*In Vivo*	TNF-*α*↓	[121]
	neutrophil elastase	10 μg/mL	*In Vitro*	N-formyl-methionyl, N-formyl-methionyl↓	[19]
Anti-AD	CL4176, CL2006, and CL2355 strains	0.25, 0.5, 1.0, 2.0 and 4.0 mg/mL	*In Vivo*	sod-3, daf-16, hsf-1, hsp-16.2, SOD↑, ROS , AChE↓	[29]
Anti-amnestic	mice	200 mg/kg	*In Vivo*	BDNF, p-CRE, p-CREB, Ser133↑, AChE↓	[126]

6. Clinical Application

As a TCM, SD had the effect of clearing heat and detoxifying, diuresis detumescence. Therefore, SD's preparations are more widely used for inflammatory diseases, skin diseases, and tumors. In this article, Chinese patent medicines or preparations, which contained SD, such as empirical prescriptions used in folklore, in-hospital preparations, and marketed drugs, are collected in Table 3.

Table 3. Chinese patent medicines or preparations containing SD

Prescription Name	Prescription composition	Functions and Treatments
Weifukang Prescription	Di ding, Pu gong ying, Huang lian, Chong lou, Bai hua she she cao, Dang shen, Shan yao, Zhe bei mu, Hai piao xiao, Zhi shi, Hou pu, Fo shou, Fu ling, Gan cao	Chronic gastritis Helicobacter pylori infection
Qiling formula	Huang qi, Ling zhi, Yi yi ren, Chen pi, Shi jian chuan, Bai hua she she cao	Chronic gastritis
Lizhong Fuyuan decoction	Bai zhu, Dan shen, Ban xia, Huang qi, Zhu ru, Chai hu, Zhi qiao, Ci wei po, Bai shao, Bai hua she she cao, Bai dou kou	Chronic gastritis
Huazhuo Jiedu Huoxue Decoction	Shi chang pu, Sha ren, Dong ling cao, Bai hua she she cao, Teng li gen, Jiang huang, E zhu, Xiang fu, Yu jin, Dang gui	Chronic gastritis
Weiduqing	Jiu bi ying, Huang lian, Ban zhi lian, Bai ying, Bai hua she she cao, E zhu, Yuan hu, Tai zi shen, Tian qi, Gan cao	Chronic gastritis Helicobacter pylori infection
Yishen Qingli Prescription	Huang qi, Shan zhu yu, Shan yao, Qian shi, Wu wei zi, Yi mu cao, Che qian cao, Bai hua she she cao, Yi yi ren, Gui jian yu, Dang gui, Hong hua, Ji xue teng	Chronic glomerulonephritis
Huimin Mixture	Tai zi shen, Huang qi, Huang qi, Mai dong, Fu ling, Di gu pi, Chai hu, Che qian zi, Gan cao, Jin yin hua, Lian zi, Bai mao gen, Yu xing cao, Ban zhi lian, Ban lan gen, Lian qiao, Bai hua she she cao, Jiang can, Ji nei jin, Shi wei, Pu gong ying, Di ding, Ban bian lian, Qing feng teng	Chronic glomerulonephritis
Yishen Jianpi Tongluo Prescription	Huang qi, Bai zhu, Tai zi shen, Qian shi, Jing ying zi, Mian bi xie, Xian he cao, Di yu tan, Bai hua she she cao, Ze xie, Fu ling, Tu fu ling, Tao ren, Di long, Gan cao	Chronic glomerulonephritis
Yishen Qingli Granules	Huang qi, Bai zhu, Shan zhu yu, Du zhong, Ze xie, Shi wei, Bai hua she she cao, San qi	Chronic glomerulonephritis
Yiqi Qufeng Huayu Qingli Prescription	Huang qi, Tai zi shen, Bai zhu, Shan zhu yu, Quan xie, Jiang can, Chan tui, Hong hua, Chuan xiong, Tu bie chong, Bai hua she she cao, Fu ling, Che qian zi	Chronic glomerulonephritis

Buqi Jiedu Decoction	Huang qi, Zhen zhu cao, Fu ling, Dan shen, Bai hua she she cao, Guan zhong, Ku shen, Yu jin, Yin yang huo, Gan cao	Chronic hepatitis B
Shugan Jianpi Jiedu Decoction	Chai hu, Huang qi, Bai shao, Dang gui, Zhi shi, Bai zhu, Xia ku cao, Bai hua she she cao, Jin yin hua, Fang feng, Gan cao	Hashimoto`s thyroiditis
Huang Gui Decoction	Dang gui, Huang bai, Jiang huang, Bai zhi, Ru xiang, Mo yao, Jin yin hua, Bai hua she she cao, Che qian cao, Chen pi	Chronic prostatitis
Keyin Xiaoban formula 1	Chong lou, Quan shen, Da qing ye, Tu fu ling, Ba qia, Bai hua she she cao, Ban zhi lian, Shan dou gen, Huang qi, Bai xian pi, Wei ling xian, Gan cao	Psoriasis
Huoxue Sanyu Xiaoyin Decoction	Dan shen, Tao ren, Hong hua, Ji xue teng, San leng, E zhu, Gui jian yu, Bai hua she she cao,Chen pi	Psoriasis
Keyin formula 1	Di huang, Mu dan pi, Chi shao, Zi cao, Bai xian pi, Ku shen, Da qing ye, Bai hua she she cao, Pu gong ying, Chan tui, Gan cao	Psoriasis
Huoxue Jiedu Decoction	Bai hua she she cao, E zhu, Gui jian yu, Hong hua, Ji xue teng, Tao ren, Dan shen, Xuan shen, Chen pi	Psoriasis
Dermatitis Flavored Soup	Di huang, Mu dan pi, Chi shao, Da qing ye, Ban lan gen, Jin yin hua, Zhi mu, Bai hua she she cao, Tu fu ling, Zi cao, Bai xian pi, Chan tui, Shi gao, Lian qiao, Ban zhi lian, Gan cao	Psoriasis
Liangxue Jiedu Pill	Shui niu jiao, Huai hua, Di huang, Chuan xiong, Huang qi, Jin yin hua, Sheng ma, Hong hua, Dang gui, Zao jiao ci, Chuan xiong, Fang feng, Qiang huo, Bai fu zi, Bai zhi, Cang zhu, Gan cao	Acne
Pipa Qingfei Decoction	Pi pa ye, Sang bai pi, Huang qi, Huang bai, Zhi zi, Dan shen, Bai hua she she cao, Yu xing cao, Da huang, Gan cao	Acne
Kecuo Decoction	Yi yi ren, Cang zhu, Ze xie, Xia ku cao, Dan shen, Ban xia, Zao jiao ci, Zhe Bei Mu, Bai hua she she cao, Shan zha, Chong lou, Gan cao	Acne
Modified Wendan Decoction	Fu ling, Chen pi, Ban xia, Zhi qiao, Zhu ru, Bai zhu, Hou pu, Bai zhi, Yi yi ren, Zao jiao ci, Zi cao, Sang ye, Mu li, Di huang, Dan shen, Bai hua she she cao□	Acne
Qingfei Loquat Danzhi Xiaoyao Powder	Pi pa ye, Huang qi, Yu xing cao, Xia ku cao, Gan cao, Dan shen, Di huang, Mu dan pi, Zhi zi, Bai shao, Fu ling, Dang gui, Chai hu, Wu zhua long, Bo he	Acne
Hedyotis diffusa Injection	Bai hua she she cao	Colorectal cancer
Kenci Semi Mixture	Dang shen, Huang qi, Bai zhu, Fu ling, Bai hua she she cao, Ban zhi lian, Shan ci gu, Yi yi ren, Xia ku cao, Zhe Bei Mu, Nv zhen zi, Gan cao	Lung cancer

Shenqi Yifei Decoction	Bei sha shen, Zhe Bei Mu, Ban zhi lian, Huang qi, Yu xing cao, Tian dong, Dang shen, Bai hua she she cao, Bai zhu, Shan zhu yu, Gan cao, Yu zhu, Nv zhen zi, Tian hua fen, Shan ci gu, Mai dong	Lung cancer
Observation of Qilian Mixture	Huang qi, Dang shen, Bai zhu, Fu ling, Bai hua she she cao, Ban zhi lian, Shan ci gu, Xia ku cao, Yi yi ren, Zhe Bei Mu, Nv zhen zi, Gan cao, Zhi mu, Mai dong, Wu wei zi□	Lung cancer
Jianpi Jiedu Decoction	Huang qi, Dang shen, Huang jing, Bai zhu, Fu ling, Yi yi ren, Bai hua she she cao, Shan yao, Chen pi, Ban xia, Gan cao	Gastric cancer

6.1. Applications for the Treatment of Chronic Gastritis

Chronic gastritis, a common digestive disorder, is primarily characterized by prolonged inflammation of the gastric mucosa [13]. The etiology of chronic gastritis is multifactorial, including irregular dietary habits, *Helicobacter pylori* infection, and drug-induced irritation [128]. TCM offers distinct therapeutic advantages in managing chronic gastritis by alleviating gastric symptoms, regulating the patient's overall constitution, and enhancing the body's resistance to disease. Treatments with TCM are generally associated with fewer side effects, making them suitable for personalized therapeutic approaches [129]. Several TCM prescriptions containing SD have been utilized in the treatment of chronic gastritis. The Weifukang Prescription, effective in addressing both chronic gastritis and *H. pylori* infection, has shown an efficacy rate of 93.1% in a cohort of 31 patients [130]. The Qiling Formula, used exclusively for chronic gastritis, exhibited a 90% success rate in 34 patients [131]. Another formulation, Lizhong Fuyuan Decoction, demonstrated a 93.5% efficacy rate in 31 patients [132]. The Huazhuo Jiedu Huoxue Decoction also treats chronic gastritis, showing a 93.75% effectiveness in 33 patients [133]. Finally, the Weiduqing Prescription, targeting both chronic gastritis and *H. pylori* infection, demonstrated the highest efficacy rate at 96.55% among 29 patients [134]. These results demonstrate the potential of TCM in the treatment of chronic gastritis, offering effective, individualized treatment options with minimal adverse effects.

6.2. Applications for the Treatment of Chronic Glomerulonephritis

Chronic glomerulonephritis, also known as chronic tubulointerstitial nephritis, is a progressive renal disorder characterized by chronic renal tubular dysfunction and potential renal failure. The condition can result from a variety of causes, including infections, medications, and immune disorders [14]. TCM has demonstrated certain advantages in the management of this disease, providing holistic benefits that improve the overall health of patients, enhance the quality of life, and help slow disease progression while reducing complications [135]. Several TCM prescriptions containing SD have been utilized in the treatment of chronic glomerulonephritis, each showing varying degrees of efficacy. The Yishen Qingli Prescription was administered to 30 patients, achieving a remarkable efficacy rate of 90% [136]. The Huimin Mixture, also given to 30 patients, demonstrated an effectiveness rate of 85.19% [137]. In a cohort of 31 patients, the Yishen Jianpi Tongluo Prescription achieved an efficacy rate of 86.21% [138]. Additionally, the Yishen Qingli Granules were used in 16 patients, showing a high success rate of 93.75% [139]. Lastly, the Yiqi Qufeng Huayu Qingli Prescription, given to 29 patients, demonstrated an efficacy rate of 93.1% [140]. These findings suggest that TCM offers a promising therapeutic approach for chronic

tubulointerstitial nephritis, with several prescriptions demonstrating significant effectiveness in clinical practice.

6.3. Applications for the Treatment of Other Inflammatory Diseases

SD is well known in TCM for its heat-clearing properties, making it an effective component in the treatment of various inflammatory diseases [123]. TCM formulations containing SD have been applied to chronic inflammatory diseases such as chronic hepatitis B, Hashimoto's thyroiditis, and chronic prostatitis, with promising clinical results. For chronic hepatitis B, the Buqi Jiedu Decoction was prescribed to 40 patients, yielding a high effectiveness rate of 92.5% [141]. The Shugan Jianpi Jiedu Decoction, used to treat Hashimoto's thyroiditis, demonstrated an impressive success rate of 96.6% in a cohort of 30 patients [142]. Meanwhile, the Huang Gui Decoction was administered to 56 patients suffering from chronic prostatitis, although the effectiveness rate was somewhat lower at 76.9% [143]. These results suggest that SD holds considerable potential in the treatment of various chronic inflammatory diseases, though further research is needed to optimise its use in different conditions.

6.4. Applications in the Treatment of Psoriasis

Psoriasis is a common chronic inflammatory skin disorder known for its recurrent nature. It is characterised by the appearance of red papules or plaques covered with layers of silvery-white scales [144]. TCM has shown remarkable benefits in the treatment of psoriasis, focusing on the overall regulation of the body's systems. TCM treatments aim to restore the balance of yin and yang, improve immune function, and address underlying imbalances, all while minimizing side effects and providing a safer alternative for long-term treatment [145]. The Keyin Xiaoban Formula 1 was prescribed to 32 patients, achieving an efficacy rate of 90.6% [146]. The Huoxue Sanyu Xiaoyin Decoction was administered to 30 patients, with a success rate of 90% [147]. A larger cohort of 48 patients received the Keyin Formula 1, although it showed a lower effectiveness rate of 77.08% [148]. The Huoxue Jiedu Decoction was given to 31 patients, resulting in a success rate of 67.74% [149]. Finally, the Dermatitis Flavored Soup was used in 34 patients, with a high efficacy rate of 90.62% [15]. These results highlight the potential of TCM prescriptions in treating psoriasis, offering promising efficacy with relatively minimal side effects.

6.5. Applications for the Treatment of Acne

Acne is a chronic inflammatory condition affecting hair follicles and sebaceous glands, often resulting in disfigurement. It is characterised by the presence of acne lesions, papules, pustules, nodules, cysts, and scarring, predominantly affecting adolescents [150]. TCM has shown significant advantages in the treatment of acne, focusing on the regulation of the body's endocrine system[151]. Through methods such as clearing heat and dampness, reducing inflammation, promoting blood circulation, and eliminating blood stasis, TCM treatments can effectively improve acne symptoms and reduce recurrence[152]. Various TCM prescriptions containing SD have been used to treat acne, with clinical data on patient numbers and effectiveness rates. The Liangxue Jiedu Pill was administered to 70 patients, achieving a success rate of 92.4% [153]. The Pipa Qingfei Decoction was prescribed to 30 patients, with a lower effectiveness rate of 70.1% [154]. The Kecuo Decoction was administered to 39 patients, resulting in a high success rate of 94.87% [155]. The Modified

Wendan Decoction was given to 31 patients, with an effectiveness rate of 86% [156]. Finally, the Qingfei Loquat Danzhi Xiaoyao Powder was used to treat 44 patients, with the highest success rate of 95.5% [157]. These prescriptions illustrate the varying effectiveness of TCM in the treatment of acne, offering promising results with a focus on holistic and individualized care.

6.6. Applications in the Treatment of Cancer

The development of tumours is characterised by uncontrolled cell growth in local tissues, resulting from various cancer-causing factors [158, 159]. TCM provides a gentler treatment option for cancer patients, with fewer side effects and a lower risk of drug resistance [160]. A key aspect of TCM is its emphasis on enhancing overall health and boosting the immune system. By enhancing the body's ability to fight cancer, TCM can also improve the patient's quality of life, making it a valuable complement to standard cancer therapies[161]. Furthermore, combining TCM with conventional Western medicine can yield better results, creating a more comprehensive and personalized treatment plan for patients [162]. Several traditional Chinese medicine prescriptions containing SD have been studied for their efficacy in improving cancer outcomes when used alongside conventional therapies. For instance, Hedyotis diffusa Injection, utilised in the treatment of colorectal cancer, demonstrated an improvement rate of 73.69% in a cohort of 38 patients [163]. The Kenci Semi Mixture, indicated for lung cancer, achieved a 73.33% improvement rate among 30 patients [164]. Similarly, the Shenqi Yifei Decoction for lung cancer showed an improvement rate of 68% in 28 patients [165]. The Observation of Qilian Mixture, also used for lung cancer, reported an improvement rate of 60.64% in 33 patients [166]. Finally, the Jianpi Jiedu Decoction, used for gastric cancer, showed an 80% improvement rate in a group of 20 patients [167]. These treatments exhibit varying degrees of effectiveness across different cancer types, underscoring the potential role of TCM in enhancing comprehensive cancer care.

7. Summary and Perspective

This review summarises the current research progress on the botany, phytochemistry, pharmacology, and clinical applications of *Scleromitrion diffusum* (SD). To date, over 259 compounds have been isolated and identified from this species, and modern pharmacological studies have demonstrated that SD possesses various significant bioactivities, including anticancer, antioxidant, anti-hepatic injury, anti-inflammatory, anti-Alzheimer's disease, anti-amnestic, and more. Nevertheless, there are several issues that require resolution for SD's further development.

First, it is important to note that the classification of the *Hedyotis-Oldenlandia* complex has been the subject of considerable controversy for a considerable period of time. SD has historically been misclassified, at times being identified as *Oldenlandia* and at other times as *Hedyotis*. However, in 2014, studies utilising phylogenetic analysis clarified its taxonomic position through phylogenetic analysis, thereby proving that SD belongs to the genus *Scleromitrion* [168]. Nevertheless, many studies continue to employ the incorrect nomenclature, thus highlighting the urgent need for standardisation.

Secondly, 259 compounds have been reported from SD, including 81 iridoids, 5 triterpenes, 28 flavonoids, 46 anthraquinones, 24 phenolic acids, 49 volatile oils, 7 polysaccharides, 3 cyclic peptides, and 16 other compounds. Among these, iridoids are the most prominent constituents, especially in recent years (Figure 2). However, research on the bioactivity of iridoids remains limited, possibly due to the scarcity of available active compounds necessary for in-depth studies.

This challenge could be addressed through chemical synthesis [169] or biosynthesis [170], facilitating further exploration of their pharmacological potential. Moreover, initial screening of compounds can be enhanced using molecular docking techniques to simulate interactions between active ingredients and target receptors, thereby increasing the efficiency of research [171].

Finally, although some progress has been made in exploring the mechanisms and pathways involved in the pharmacological activities of SD, the majority of studies continue to focus on the effects of different extracts [119, 121]. The specific compounds responsible for these activities have yet to be fully elucidated. However, with the rise of network pharmacology, it is anticipated that this gap could be bridged, offering new insights into the material basis of SD's therapeutic actions.

In conclusion, SD is a promising herb with diverse applications and significant medical value. In vitro and in vivo pharmacological studies have progressively validated and modernized the mechanisms underlying its traditional uses. The advent of new technologies has created significant potential for further medicinal research and the development of new applications for SD.

Author contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Funding

This work was supported by Shanghai Pudong New District Health Committee's Key Disciplines of Clinical Pharmacy (grant number PWZxk2022-26).

Competing Interests

The authors declare that there is no conflict of interest.

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